

Ultra-Processed Foods Consumption, Depression, and the Risk of Diabetes and its Complications in a Population-Based Sample

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Abstract

Worldwide, type 2 diabetes mellitus (T2D) is an increasingly prevalent chronic disease and a public health concern. Unhealthy diets, such as those with high ultra-processed foods (UPF) consumption, have been identified as one of the behavioral risk factors related to T2D and its consequences. Depression is a serious mood disorder commonly comorbid with diabetes and a potentially modifiable risk factor for T2D. Previous studies have focused on depression and unhealthy diets consumption as independent risk factors for T2D and its complications, but unhealthy diets and depression might also be comorbid. Therefore, in this thesis, I will examine the interaction between depression and UPF and its association with T2D and its complications.

In this study, the research question was “What is the relationship between T2D, UPF consumption, and depressive symptoms?” Data from the CARTaGENE a population-based prospective cohort study in the Province of Quebec (Canada), were used to address this question by completing three independent but related studies shaped by research objective and presented in standalone chapters (3, 4, and 5). CARTaGENE and an administrative health database (Quebec’s health care plan), were linked to generate the study sample.

The first objective was to explore the potential additive interaction between UPF consumption and depression on the *incidence* of T2D. Results of Cox regression modelling showed that respondents with high depressive symptoms and high UPF consumption at the baseline showed the highest risk for T2D (Hazard Ratio (HR) = 1.75 (95 % CI 1.04 - 2.95)) in a model adjusted for age and sex compared to respondents with low depressive symptoms and low UPF consumption. Further, the risk for T2D when high depressive symptoms and antidepressant use were combined with high UPF was HR = 1.62 (95 % CI 1.02 - 2.57) in a fully adjusted model.

The second objective was to investigate a potential additive interaction between UPF consumption and depression on the *incidence* of diabetes-related complications. Data from the same cohort as in the first study were used. However, for this objective, we examined the T2D complications among respondents with T2D at baseline by linking CARTaGENE survey data with administrative health care plan data. Results by a Cox regression model indicate that individuals with depressive symptoms and higher UPF consumption at baseline had a higher risk (HR = 2.43 (95 % CI 1.18 - 4.99)) of developing T2D related micro-and macro complications in a model adjusted for sex and age compared to those with neither condition. Further, higher risks for diabetes complications were observed when high depressive symptoms and antidepressant use were combined with high UPF consumption (HR = 2.59 (95 % CI 1.32 - 5.06)) in a fully adjusted model. These results suggest an interaction between depression and UPF consumption in relation to an increased risk of diabetes-related complications.

Finally, although depression has been linked with T2D incidence, the underlying mechanism remains unclear. The third objective was thus to explore if the relationship between depression and T2D incidence might be *mediated* by UPF consumption. Using logistic regression and mediation analysis, we found that a retrospectively reported depression diagnosis was associated with a higher risk of T2D (Odd ratios = 1.58 (95 % CI 1.05 - 2.36)). Further, UPF consumption and Body Mass Index (BMI) at baseline might be an indirect mechanism linking depression and T2D risk.

Overall, the results showed that individuals with co-occurring depression and high UPF consumption might represent a subgroup particularly vulnerable to T2D incidence and its complications. They would benefit from improved identification, greater monitoring, and

preventive, integrated care that draws on strategies embracing the newly generated evidence on the interaction between T2D, depression, and UPF consumption.

Résumé

À l'échelle mondiale, le diabète de type 2 (DT2) est une maladie chronique de plus en plus répandue et un problème de santé publique préoccupant. Les régimes alimentaires inadéquats tels que ceux caractérisés par une forte consommation d'aliments ultratransformés, ont été identifiés comme l'un des facteurs de risque comportementaux liés au DT2 et à ses complications. La dépression, un trouble de l'humeur grave, est une comorbidité courante du diabète et un facteur de risque potentiellement modifiable du DT2. Les études antérieures se sont concentrées sur la dépression et les régimes alimentaires inadéquats en tant que facteurs de risque indépendants pour le DT2 et ses complications, mais il se peut également que les régimes alimentaires inadéquats et la dépression soient comorbides. Par conséquent, dans cette thèse, j'examinerai l'interaction entre la dépression et la consommation d'aliments ultratransformés et l'association entre cette interaction et le développement du DT2 et de ses complications.

Dans cette étude, la question de recherche était la suivante: "Quelle est la relation entre le DT2, la consommation d'aliments ultratransformés et les symptômes dépressifs ?" Les données de l'étude de cohorte prospective CARTaGENE, basée dans la province de Québec (Canada), ont été utilisées pour répondre à cette question en réalisant trois études indépendantes mais liées, présentées dans des chapitres séparés (3, 4 et 5). CARTaGENE et une base de données administrative en santé (le plan de soins de santé du Québec) ont été reliés pour constituer l'échantillon de l'étude.

Le premier objectif était d'explorer l'interaction additive potentielle entre la consommation d'aliments ultratransformés et la dépression sur l'incidence du DT2. Les résultats de la modélisation par régression de Cox ont montré que les répondants présentant des symptômes dépressifs élevés et une forte consommation d'aliments ultratransformés au début de

l'étude présentaient le risque le plus élevé de développer un DT2 (rapport de risque instantané (HR) = 1,75 (IC à 95 % 1,04 - 2,95)) dans un modèle ajusté en fonction de l'âge et du sexe, par rapport à ceux présentant des symptômes dépressifs faibles et une faible consommation d'aliments ultratransformés. De plus, le risque de T2D en cas de symptômes dépressifs élevés et d'utilisation d'antidépresseurs combinés à une forte consommation d'aliments ultratransformés était de HR = 1,62 (IC à 95 % 1,02 - 2,57) dans un modèle entièrement ajusté.

Le deuxième objectif était d'examiner une interaction additive potentielle entre la consommation d'aliments ultratransformés et la dépression sur l'incidence des complications liées au diabète. Les données provenant de la même cohorte que dans la première étude ont été utilisées. Cependant, pour cet objectif, nous avons examiné les complications liées au DT2 parmi les répondants atteints de DT2 au début de l'étude en reliant les données de l'enquête CARTaGENE aux données du plan de soins de santé administratif. Les résultats d'un modèle de régression de Cox indiquent que les individus présentant des symptômes dépressifs et une consommation élevée d'aliments ultratransformés au début de l'étude présentaient un risque plus élevé (HR = 2,43 (IC à 95 % 1,18 - 4,99)) de développer des complications micro et macrovasculaires liées au DT2, dans un modèle ajusté en fonction du sexe et de l'âge, par rapport à ceux ne présentant aucune de ces conditions. De plus, des risques plus élevés de complications liées au diabète ont été observés lorsque des symptômes dépressifs élevés et l'utilisation d'antidépresseurs étaient combinés à une forte consommation d'aliments ultratransformés (HR = 2,59 (IC à 95 % 1,32 - 5,06)) dans un modèle entièrement ajusté. Ces résultats suggèrent une interaction entre la dépression et la consommation d'aliments ultratransformés pour une augmentation du risque de complications liées au diabète.

Enfin, bien que la dépression ait été liée à l'incidence du DT2, le mécanisme sous-jacent reste peu clair. Le troisième objectif était donc d'explorer si la relation entre la dépression et l'incidence du DT2 pourrait être médiée par la consommation d'aliments ultratransformés. En utilisant la régression logistique et l'analyse de médiation, nous avons trouvé qu'un diagnostic de dépression rapporté rétrospectivement était associé à un risque plus élevé de DT2 (rapport de cotes = 1,58 (IC à 95 % 1,05 - 2,36)). De plus, il se pourrait que la consommation d'aliments ultratransformés et l'indice de masse corporelle (IMC) au début de l'étude soient un mécanisme indirect liant la dépression et le risque de DT2.

En résumé, les résultats montrent que les individus présentant une dépression coexistante et une forte consommation d'aliments ultratransformés pourraient constituer un sous-groupe particulièrement vulnérable au développement du DT2 et de ses complications. Ils bénéficieraient d'un meilleur dépistage, d'une surveillance accrue et de soins préventifs intégrés s'appuyant sur des stratégies tirant parti des nouvelles preuves générées sur l'interaction entre le DT2, la dépression et la consommation d'aliments ultratransformés.

Contribution to Knowledge

The work presented in this doctoral dissertation makes a meaningful contribution to understanding the associations between depression, ultra-processed food (UPF) consumption, and the risk of type 2 diabetes (T2D) and its complications. Nominal research examines these associations in a population-based cohort, as most studies focus on either depression or ultra-processed foods but not both. The three manuscripts presented in this dissertation add evidence to the literature by examining how depression and UPF consumption, when present in combination, can influence the risk estimate for developing T2D and its complications. Evidence is added regarding the mechanism between depression, UPF, and T2D.

Although there is an established individual association between depression, unhealthy food consumption, and risk of T2D, no prior work has prospectively investigated the potential additive interaction between UPF consumption and depression on the incidence of T2D. The first manuscript published in the *Journal of Public Health Nutrition* assesses how these two modifiable risk factors, when present at the same time, can influence diabetes risk. Evidence shows that the risk for T2D incidence was high for individuals with both elevated depression and high UPF consumption at baseline. Manuscript 1 highlights the interaction between UPF consumption and depression as potentially modifiable risk factors for T2D.

Manuscript 2 extends the results from Manuscript 1 by examining the association between depression, UPF consumption, and the risk of T2D complications. The results of manuscript 1 confirmed that participants with both elevated depression and high UPF consumption at baseline were at an increased risk of developing T2D. As a next step, manuscript 2 assessed how these risk factors can influence diabetes-related complications. Similar to

manuscript 1, results provide novel information that when depression and high UPF consumption co-occur, the risk of diabetes complications is greater.

Finally, there is evidence that depression is associated with T2D through various health-related behaviors. However, it is not clear how much UPF consumption and body mass index (BMI) contribute to this relationship. In manuscript 3, UPF consumption and BMI were assessed as potential mediators of the association between depression and T2D. Results suggest that depression may partly be related to T2D incidence via UPF consumption and BMI.

Overall, this dissertation advances scientific knowledge by elucidating the association between depression and the incidence of T2D and its complications by investigating the role of UPF. Further, results could contribute to clinical advancement by identifying individuals at high risk of T2D and its related complications.

Published research articles in peer-reviewed journals

- **Sen, A.,** Brazeau, A. S., Deschênes, S., Melgar-Quiñonez, H. R., & Schmitz, N. (2022). The role of ultra-processed food consumption and depression on type 2 diabetes incidence: a prospective community study in Quebec, Canada. *Public Health Nutrition*, 1-10. DOI: <https://doi.org/10.1017/S1368980022002373>

Published Abstracts

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- **Sen, A.,** Schmitz, N., Brazeau, A. S., Deschênes, S., & Melgar-Quinonez, H. R. The Role of Ultra-Processed Food and Depression on the Incidence of Type 2 Diabetes: A Community Study from Quebec, Canada. Canadian Journal of Diabetes. 2021 Nov 1;45(7): S27-8. <https://doi.org/10.1016/j.jcjd.2021.09.083>
- **Sen, A.,** Schmitz, N., Brazeau, A. S., Deschênes, S., & Melgar-Quinonez, H. R. Associations between ultra-processed food consumption, depression, and incidence of diabetic complications: A prospective community study in Quebec, Canada. Appl.Physiol.Nutr.Metab.Vol.47,2022, S39
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Contribution of Authors

For the first manuscript, the candidate conceived the research question, designed the study, performed the analyses, interpreted the findings, and wrote the manuscript. Dr. Norbert Schmitz acquired the data and provided academic supervision, intellectual input, and methodological and theoretical guidance. Dr. Melgar Quinonez provided significant academic supervision and critical inputs on the presentation and interpretation of results and revision of the draft manuscript. Dr. Sonya Deschenes and Dr. Anne-Sophie Brazeau provided methodological expertise and critically reviewed the manuscript. All the authors reviewed and approved the final manuscript.

For the second manuscript, the candidate conceived the research question, designed the study, performed the analyses, and interpreted the findings with significant help and direction from Dr. Norbert Schmitz. The candidate drafted the manuscript as well as the subsequent revisions. Dr. Melgar Quinonez, Sonya Deschenes, and Dr. Anne-Sophie Brazeau provided significant help with data presentation and interpretation. All the authors reviewed and approved the final manuscript.

For the third manuscript, the candidate conceived the research question, designed the study, performed the analyses, interpreted the findings, and wrote the manuscript with significant help and direction from Dr. Norbert Schmitz. Dr. Melgar-Quinonez and Dr. Sonya Deschenes provided methodological expertise and critically reviewed the manuscript. All the authors reviewed and approved the final manuscript.

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List of Abbreviation

aHR	Adjusted Hazard Ratios
ADA	American Diabetes Association's
AGEs	Advanced glycation end products
AHEI	Alternative Healthy Eating Index
APA	American Psychiatric Association
BMI	Body Mass Index
CaG	CARTaGENE
CANRISK	Canadian Diabetes Risk Questionnaire
CCHS	Canadian Community Health Survey
C-DHQ II	Canadian-Diet History Questionnaire II
CES-D	Centre for Epidemiologic Studies – Depression
CI	Confidence intervals
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
CVD	Cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
DSME	Diabetes Self-Management Education
ENSANUT	Encuesta Nacional de Salud y Nutrición
FFQ	Food Frequency Questionnaire
HADS	Hospital Anxiety and Depression Scale
HELFIMED	Healthy Eating for Life with a Mediterranean Diet

HPA	Hypothalamic-Pituitary-Adrenal
HR	Hazard Ratios
HUD	Higher tertile of UPF consumption and high depressive symptoms
HUDA	Higher tertile of UPF consumption and high depressive symptoms or antidepressant use
HUND	Higher tertile of UPF consumption and low depressive symptoms
IL	Interleukin
ICD	International Statistical Classification of Diseases
LUD	Lower/middle tertile of UPF consumption and high depressive symptoms
LUDA	Lower/middle tertile of UPF consumption and high depressive symptoms or antidepressant use
LUND	Lower/middle tertile of UPF consumption and low depressive symptoms
LUNDA	Lower and middle tertile of UPF consumption and low depressive symptoms and no antidepressant use
MDD	Major depressive disorder
MPD	Mediterranean Dietary Pattern
OR	Odd Ratios
PHQ-9	PHQ-9 - Patient Health Questionnaire 9
RAMQ	Régie de l'Assurance Maladie du Québec
RCTs	Randomized controlled trials
RERI	Relative excess rate due to interaction
RR	Relative risk
SMILES	Supporting the Modification of lifestyle in Lowered Emotional States

T2D	Type 2 diabetes mellitus
TNF-α	Tumour Necrosis Factor alpha
U.S.	United States
UPF	Ultra-processed foods
WHO	World Health Organization's

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Chapter 1: Introduction

Background and Rationale

The World Health Organization's (WHO) *Global Action Plan for the Prevention and Control of Non-Communicable Diseases* aims to reduce premature mortality from chronic diseases by 25% by 2025 (WHO, 2013). Worldwide, type 2 diabetes mellitus (T2D) constitutes an increasingly prevalent chronic disease representing a substantial public health concern. T2D occur when either insulin is not produced enough or there is insulin resistance. Untreated, there eventually is too much sugar circulating in the blood leading to disorders affecting the circulatory, nervous, and immune systems (WHO, 2013).

Diabetes is also a prevalent health issue in Canada, affecting approximately 3 million Canadians (about 8% of the population). Upwards of 95% of diabetes cases are T2D (LeBlanc et al., 2019). The etiology of T2D is multifactorial and influenced by the interplay of biological, genetic, sociodemographic, psychosocial, psychological, and behavioral factors. This study is interested in the potential connection between T2D, depression, and dietary habits (especially ultra-processed foods [UPF] consumption) based on the assumption that they are interrelated.

Depression is a serious mental health problem characterized mainly by low (despondent) mood and aversion to or loss of pleasure with or interest in activity. It affects thoughts, feelings, behavior, and one's sense of well-being for long periods of time (Rehm & Shield, 2019; WHO, 2023). Depression is commonly comorbid with T2D and has been identified as a potential risk factor for T2D morbidity and mortality. Research from longitudinal studies has shown that depression might increase the risk of T2D incidence by 40–60 % (Nouwen et al., 2019). In general, depression is often unrecognized and untreated in two-thirds of the population suffering from diabetes, which may exacerbate the risk of microvascular and macrovascular complications

in people with T2D (Nouwen et al., 2019). While some individuals with depression may never develop T2D and its related complications, others will. Therefore, more evidence is needed to understand better when and under what conditions depression increases the risk of developing T2D and its complications (e.g., eye, feet, and kidney problems; heart attack and stroke and related conditions such as nerve damage).

Clinical and epidemiological studies have provided persuasive evidence that lifestyle behaviors, such as weight management, eating a healthy diet, and regular physical activity, can prevent or delay the onset of diabetes (Tabák et al., 2014). Healthy diets are a cornerstone lifestyle intervention for managing diabetes (Schlesinger et al., 2020). Unhealthy diets, such as those high in ultra-processed foods (UPF) consumption, typically involve the intake of food products that have undergone extensive industrial processing and contain additives, preservatives, and often high levels of refined sugars, unhealthy fats, and salt (Monteiro et al., 2019a). Diets high in UPF often lack essential nutrients and fiber while being energy dense. UPF represent a growing proportion of the world's food supply and have shown to be an important predictor of poor health outcomes (Monteiro et al., 2019a). Recent evidence suggests that UPF makes close to 50% of the calories consumed on average by Canadian on a daily basis (Moubarac et al., 2017). These foods are also an important predictor for both depression (Mazloomi et al., 2022) and T2D (Nardocci et al., 2021).

UPF are high in inflammatory markers such as C-reactive protein (CRP), Tumour Necrosis Factor alpha (TNF- α), Interleukin (IL)-1 and IL-6 levels (Lopes et al., 2019) and can increase the risk of T2D independently of the Body Mass Index (BMI) (body fat measurement based on height and weight) and other diabetes risk factors (Delpino et al., 2022). Further, a meta-analysis of prospective studies has shown that higher UPF consumption could increase the

risk of depression (Mazloomi et al., 2022). Depressive symptoms are associated with these inflammatory markers as well (Tabák et al., 2014). Therefore, it is possible that depression and UPF consumption may exacerbate a common pathway resulting in a substantially elevated risk for T2D incidence and its complications.

Previous studies have focused on depression and diet as independent risk factors for T2D and its complications. Depression and diet are not independent; there is evidence for a bidirectional relationship between them (Beydoun et al., 2016). According to the American Psychiatric Association (APA) (1980), a decrease or increase in appetite is also a symptom of depression as described in the Fifth Edition of the *Diagnostic and Statistical Manual of Mental Disorders*. Through changes in brain functioning, depression might influence appetite and food choices by leading people to prefer an unhealthy diet (Simmons et al., 2016). One explanation is that individuals with depression may choose high-fat-high-sugar food to ameliorate unpleasant affective states through the stimulation of the reward system (Weltens et al., 2014). These reward responses can drive the loss of self-control leading to overeating and subsequent weight gain, which in turn leading to the development of T2D (Alonso-Alonso et al., 2015). Studies have reported associations between depressive symptoms and consumption of foods high in sugar or salt (Weltens et al., 2014), with a significant proportion of such foods falling under the category of UPF. UPFs, characterized by extensive industrial processing, often contain elevated levels of free sugars, unhealthy fats, and salt (Monteiro et al., 2019a). Moreover, the link between high frequency sugar intake and the development of T2D has been well-established in existing research (Veit et al., 2022).

Further, depression among T2D individuals is often associated with poorer adherence to lifestyle and dietary recommendations, poorer diabetes management, and non-adherence to

diabetes medication (Tabák et al., 2014). These behaviors might add more detrimental effects in the context of diabetes, possibly resulting in poor glycemic control, which, in turn, may be associated with an increased risk of diabetes complications (Nouwen et al., 2019).

Statement of Purpose and Research Question

Although previous research has independently shown associations between depressive symptoms, UPF consumption, and the onset of T2D and T2D complications, an important next step is to understand better the interaction between depressive symptoms and UPF consumption and its association with T2D and T2D complications. Moreover, less is known about the potential influence of depression on the UPF consumption and how it influences T2D incidence. It is also possible that UPF consumption mediates some of the associations between depression and T2D. The research question guiding this study was thus “*What is the relationship between T2D and UPF consumption and depressive symptoms?*”

Research Objectives and Hypotheses

This manuscript-based dissertation includes three research objectives, and each objective is presented as a separate study in a standalone manuscript in a separate chapter (Chapters 3, 4, and 5). Chapter 2 includes an overall literature review with each of Chapters 3, 4, and 5 containing its respective literature review section. Chapter 6 is dedicated to the discussion, implications, and conclusions.

Research Objective 1, Manuscript 1: Chapter 3

The first research objective is to prospectively investigate the potential additive interaction between UPF consumption and depressive symptoms on the incidence of T2D in a Canadian community sample.

Hypothesis 1: Individuals with both high depressive symptoms and high UPF consumption at baseline would have a higher risk of developing T2D than those with high depressive symptoms only and with high UPF consumption only or neither.

Research Objective 2, Manuscript 2: Chapter 4

The second research objective is to investigate a potential additive interaction between UPF consumption and depressive symptoms on the incidence of diabetes-related complications in adults with T2D.

Hypothesis 2: Individuals with T2D with both depressive symptoms and high UPF consumption at baseline would have a higher risk of developing diabetes-related micro-and macrovascular complications compared to those without depressive symptoms and with low UPF consumption.

Research Objective 3, Manuscript 3: Chapter 5

The third research objective is to estimate how much UPF consumption contributes to the relationship between depression and T2D incidence. Further, this study assesses if UPF is still a mediator when considering a potential mediating effect of BMI on the association between depression and diabetes onset.

Hypothesis 3: (i) Depression will be associated with T2D incidence, and (ii) UPF consumption will be a substantial mediating factor between depression and T2D.

Chapter 2: Literature Review

Pursuant to the research question, this general literature review dealt with three topics: Type 2 diabetes (T2D), depression, and ultra-processed foods (UPF). The supportive list of references is at the end of the thesis.

Type 2 diabetes

Epidemiology of Type 2 Diabetes

Diabetes mellitus is a prevalent chronic metabolic disorder representing a substantial public health concern. It occurs when the pancreas no longer produces enough insulin or because of insulin resistance, which is required to maintain blood sugar levels. The majority of diabetes cases can be broadly classified into three categories: (a) Type 1 diabetes is an auto-immune disease characterized by autoimmune-mediated pancreatic β -cell destruction leading to absolute insulin deficiency, which generally developed during childhood and adolescence; (b) Gestational diabetes occurs at the time of pregnancy and often disappears after delivery; and (c) Type 2 diabetes (T2D) is a metabolic condition characterized by peripheral insulin resistance (i.e., liver, muscles, and adipose tissue) and deficient β -cell insulin secretion leading to relative insulin deficiency (Punthakee et al., 2018).

At present, the world is facing a significant health concern related to diabetes. It has been estimated that the 2021 global prevalence of diagnosed diabetes among the adult population (20–70 years) was 537 million. This number is predicted to rise to 783 million by 2045. Moreover, the number of individuals with diabetes is expected to be larger than such estimates when considering undiagnosed cases, and it is projected that 240 million adults worldwide are living with undiagnosed diabetes cases (Sun et al., 2022). Further, as of 2021, according to the Canadian Diabetes Association (now called Diabetes Canada), approximately 3 million

Canadians were living with diagnosed diabetes, and it is estimated that an additional 1.5 million have undiagnosed diabetes (Public Health Agency of Canada, 2022). Moreover, a recent study conducted in Quebec, Canada, highlighted that in 2019, the prevalence of diabetes in the region reached 8.1%, affecting more than 675,000 residents. Over the period from 2001 to 2019, positive trends were observed, including a decline in both the incidence of diabetes and all-cause mortality. The age-standardized prevalence exhibited a stabilization during the same timeframe. However, there was a concerning 25% increase in diabetes incidence among individuals aged 1–19 years (O’Connor et al., 2023).

Consequences of Type 2 Diabetes

Individuals with diabetes are at increased risk of both premature morbidity and premature mortality. Much of the global burden of T2D is due to the development of diabetes complications (Van et al., 2010; Zheng et al., 2018). Globally, it is estimated that in 2021, approximately 6.7 million adult deaths could be attributed to diabetes or to its complications (Sun et al., 2022).

High-level blood glucose over time can lead to an increased risk of microvascular and macrovascular complications, all of which affect a patient’s health, productivity, and quality of life (Van et al., 2010). Conditions that damage the body’s smaller blood vessels are categorized as microvascular complications, such as retinopathy, neuropathy, and nephropathy (i.e., eyes, kidney, and nerves). In contrast, conditions that result from damage caused to the body’s larger blood vessels due to fat or plaque buildup are known as macrovascular complications, leading to cardiovascular disease (CVD) (Forbes & Fotheringham, 2017; Zheng et al., 2018).

Macrovascular complications (e.g., high blood pressure, arrhythmias, and arterial stiffness) remain the predominant cause of accelerated mortality in T2D (Nwaneri et al., 2013). CVD,

mainly related to coronary heart disease and heart attacks, is responsible for at least 50% of mortality in people with diabetes (Sun et al., 2022).

In Canada, mortality rates among individuals with diabetes are almost twice as high as those without diabetes (1,021 deaths per 100,000 people with diabetes vs. 520 per 100,000 without diabetes). Even though between 2000 and 2016 the mortality rate among adults with diabetes decreased, it still remained higher than the general population (LeBlanc et al., 2019). At the global level, overall mortality and rates of diabetes complications have also lowered in individuals with diabetes in recent years, which can be attributed to improved management of risk factors (e.g., hyperglycemia, hypertension, and dyslipidemia) and improved diabetes care (Færch et al., 2014; Forbes & Fotheringham, 2017). Nonetheless, due to the increasing rate of diabetes, the number of individuals with diabetes complications is still rising globally (Forbes & Fotheringham, 2017).

Type 2 Diabetes and Risk Factors

Prospective cohort studies have identified various non-modifiable and modifiable risk factors associated with the development of T2D. Among others, non-modifiable risk factors include aging and a family history of diabetes (Diabetes Canada and Diabètes Québec, 2000; Kaczorowski et al., 2009). Modifiable risk factors include low physical activity, low-quality diet, smoking, depression, prediabetes, abdominal obesity, and high blood pressure, some of which are manifestations of metabolic syndrome (Charles et al., 1991; Eastman et al., 1997; Prebtani et al., 2018; Rotella & Mannucci, 2013; Tuomilehto et al., 1992).

As explained below, healthy diets are considered a cornerstone lifestyle factor playing an important role in overall health status. Poor dietary quality seems to play a significant role in escalating the T2D epidemic worldwide. Clinical and epidemiological studies have provided

persuasive evidence that a healthy diet can prevent or delay the onset of diabetes and its complications (de Lorgeril & Salen, 2015; Pan et al., 1997; Tabák et al., 2014). In addition, other research studies have supported the relationship between dietary habits and T2D (see Afshin et al., 2019). Afshin's study (2019) evaluated global dietary consumption patterns across 195 countries and revealed that suboptimal diets constituted a significant contributor to death compared to any other risk factors; T2D was among the top three diseases and leading diet-related cause of mortality.

Furthermore, a recent review showed that a balanced diet providing macro- and micronutrients to meet an individual's daily nutrient requirements reduced CVD risk in individuals with diabetes (Archundia Herrera et al., 2017). Prospective cohort studies have supported diets of high dietary quality: the Alternative Healthy Eating Index (AHEI), the alternate Mediterranean Dietary Pattern (MPD), Dietary Approaches to Stop Hypertension (DASH), and the American Diabetes Association's (ADA) recommended diets, which showed a significantly lower risk of CVD incidence and CVD mortality among adults with T2D (Hirahatake et al., 2019; Liu et al., 2018). Further, various studies have shown an inverse association between higher diet quality and risk of microvascular complications such as nephropathy, retinopathy, and neuropathy, which are common in T2D (El Bilbeisi et al., 2017).

In contrast, a diet characterized by a high intake of red meat, sugar, carbohydrates, and fried foods contributes to an elevated risk of insulin resistance and T2D (Sami et al., 2017). Specifically, the consumption of added sugars, especially refined sugars, and sugary beverages, has been linked to an increased likelihood of weight gain, obesity, insulin resistance, and subsequently, the development of T2D (Sami et al., 2017).

Obesity and being overweight are well-established risk factors for T2D incidence. In a meta-analysis of prospective cohort studies, the overall relative risk (RR) of diabetes for obese individuals was seven times higher (RR 7.19, 95% CI: 5.74 -9.00) compared to those with normal weight, while the risk for diabetes in overweight individuals was three times higher (2.99, 95% CI: 2.42 -3.72) (Abdullah et al., 2010).

Socioeconomic factors might also be associated with diabetes, as diabetes is more prevalent among Canadians with lower education and low-income levels, and adults living in more deprived neighborhoods (Booth et al., 2013; Brown et al., 2015). According to the *Canadian Community Health Survey*, the prevalence of T2D in the lowest-income group is four times higher than in the highest-income group. The low-income group is at a 77% higher risk of developing T2D (HR= 1.77, 95%CI: 1.48–2.12) (Dinca-Panaitescu et al., 2012).

One reason for this association might be related to limited access to healthy foods. Individuals with low income may have limited access to affordable, nutritious foods, particularly fresh fruits, vegetables, and whole grains (Marcy et al., 2011). This deprivation can lead to a higher consumption of high-calorie processed foods, unhealthy fats, and added sugar thereby increasing the risk of developing obesity and T2D (Al-Jawaldeh & Abbass, 2022).

Depression

Epidemiology of Depression

Psychosocial factors, including depression, are also considered risk factors for T2D (Tabák et al., 2014). Depression is associated with an increased risk of T2D similar in magnitude to (a) smoking (meta-analyzed RR for diabetes 1.60 (95% CI 1.37-1.88)) (Mezuk et al., 2008); (b) physical inactivity 1.20 (95% CI 1.11-1.33) (Lee et al., 2012); and (c) current smoking 1.44 (95% CI 1.31-1.58) (Willi et al., 2007).

Depression is a common and complex mood disorder characterized by sadness, loss of interest in activities for long periods of time, or both. It is recognized as a global public health concern (Rehm & Shield, 2019). According to the WHO (2023), approximately 280 million people suffer from depression globally. The *Global Burden of Disease* recently projected depressive disorders as one of the most significant contributors to global disability (2nd rank) and to diminished active life expectancy (11th rank) (Rehm & Shield, 2019). According to the 2012 *Canadian Community Health Survey–Mental Health*, the annual prevalence of depressive disorder in Canada was 4.7% (Patten et al., 2015). Moreover, the COVID-19 pandemic negatively impacted mental health globally, including in Canada. Data from eight Canadian provinces revealed that the prevalence of major depressive disorder (MDD) in 2020 doubled the pre-COVID times prevalence estimate (16% vs. 7% respectively) (Shields et al., 2021).

Measures of Depression

Clinical depression, such as MDD and major depressive episodes, can be diagnosed using standardized criteria defined by the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) and the *International Statistical Classification of Diseases* (ICD-10) (Sarmiento & Lau, 2020). Symptoms include depressed mood, disinterest in everyday activities, body weight or appetite change, change in sleep patterns, psychomotor agitation, fatigue or loss of energy, feelings of guilt or worthlessness, difficulty in concentrating, and thoughts of death or suicide. Symptoms of either a depressed mood or loss of interest or pleasure in everyday activities are present. A total of five or more of these symptoms must be identified for a formal diagnosis of clinical depression (Sarmiento & Lau, 2020).

The gold standard instrument for the diagnosis of depression is a semi-structured diagnostic interview administered by a clinician, for example, a *Structured Clinical Interview for*

DSM. In epidemiological research, it is less common to conduct semi-structured diagnostic interviews because they are time consuming and require trained professionals (Gelaye et al., 2014). Fully structured interviews are also used to assess depression; these methods also use the criteria from the DSM or ICD, but do not include the clinician's judgment (Levis et al., 2018).

Further, depression can be evaluated using depressive symptom scales, diagnoses of depression, and evidence of antidepressant medication use. In epidemiological studies, symptom scales such as the *Patient Health Questionnaire 9* (PHQ-9) (Kroenke et al., 2001), the *Centre for Epidemiologic Studies – Depression* (CES-D) (Radloff, 1977) and the *Hospital Anxiety and Depression Scale* (HADS) are often used to assess depression (Zigmond & Snaith, 1983).

In this thesis, depressive symptoms were evaluated using PHQ-9, which is a self-administered, nine-item screening questionnaire. The questions are related to vegetative, emotional, behavioral, and cognitive symptoms during the two weeks prior to the interview (For more detailed information on the specific questions included in the PHQ-9 questionnaire, please refer to Appendix 4). Responses range from 'not at all' (0) to 'every day' (3) with a summary score ranging from 0 to 27. PHQ-9 is an easily administered and nine symptom items directly aligned with the criteria for a major depressive episode in the Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition (He et al., 2020). Extensive research has demonstrated the accuracy of the PHQ-9 in identifying major depression across various settings and patient populations (He et al., 2020). It is widely used and validated in different populations, including Quebec, Canada (Arthurs et al., 2012). The PHQ-9 has a sensitivity of 88% and a specificity of 78% when compared to semi- and fully structured interviews (Kroenke et al., 2001; Pettersson et al., 2015). Antidepressant use can also provide insights into the prevalence and treatment of depression, as antidepressants are commonly prescribed for managing depressive symptoms

(Delgado, 2004). The prevalence of antidepressant prescriptions in Canada increased from approximately 9.2% in 2006 to 12.8% in 2012 (Morkem et al., 2015), a 40% increase in less than a decade. Of note is that, in Canada, antidepressants can also be prescribed for other health issues such as anxiety, insomnia, pain, and other mental health disorders (Wong et al., 2016).

Administrative data can provide further information on the diagnosis of depression. Those include diagnostic and procedural codes obtained from encounters with the healthcare system including physician visits, prescriptions, and surgeries/procedures (Townsend et al., 2012). The case definition “two depression claims within one year or one Discharge Abstract Data diagnosis” can be used for depression in administrative data resulting in a moderate level (61%) sensitivity with a high specificity (94.3%). In British Columbia and Alberta in 2001–2004, the prevalence of depression diagnoses through medical charts was estimated in 15.9% and 19.2%, respectively (Doktorchik et al., 2019).

Contributing Factors to Depression

Depression is a complex condition influenced by a variety of factors. As mentioned, it is often the result of a complex interaction of social, psychological, and biological factors. Individuals who have gone through adverse life events, such as unemployment, bereavement, and traumatic events, are more likely to develop depression. A meta-analysis using representative samples from 53 countries participating in the *World Health Surveys* found that fewer material assets, lower education, economic inactivity, and being divorced or widowed were associated with increased odds of depression episodes (Rai et al., 2013).

In Canada, financial strain and low income were associated with the incidence of new major depressive episodes (Rai et al., 2013). In contrast, the prevalence of depression was lower in adults in higher income groups (Patten et al., 2015). Furthermore, the prevalence of depression

is approximately 18% higher in urban compared to rural regions of Canada (Wiens et al., 2017). Women are more likely than men to experience depression. In Canada, the prevalence was 5.0% in women and 2.9% in men in 2002 (1.7-fold greater incidence in women). This increased respectively to 5.8% and 3.6% in 2012 (Patten et al., 2015; Pearson et al., 2013).

Negative health-related behaviors such as eating a poor-quality diet, reduced physical activity or sedentariness, and smoking can be determinantal to depression (Teychenne et al., 2010). Diet high in UPF, have been linked to an increased risk of depression and are discussed below (Mazloomi et al., 2022). In fact, dietary intervention studies (healthy diet) have shown positive impacts in clinical depression and depressive symptoms. To illustrate, two randomized controlled trials (RCTs) in adults with current depression have consistently observed moderate-to-large symptom improvements by following the Mediterranean diet-based interventions. Both the *Supporting the Modification of lifestyle in Lowered Emotional States* (SMILES) trial and the *Healthy Eating for Life with a Mediterranean Diet* (HELFIMED) trial reported significant reductions in depressive symptoms following adjunctive Mediterranean diet interventions in adults with depression compared to subjects in control groups (Jacka et al., 2017; Parletta et al., 2019).

Furthermore, like diet, physical inactivity is also a modifiable risk factor for depression. A meta-analysis of prospective studies supports the notion that physical activity can confer protection against the emergence of depression regardless of age (Schuch et al., 2018).

Moreover, individuals with depression often engage in more than one of these negative health related behaviors (Verger et al., 2009), which can increase the risk of obesity, which is also a well-established risk factor for depression. The relationship between diet, depression, and obesity is bi-directional and complex. Meta-analytic data have shown that both men and women

with obesity have a 55% increased risk of developing depression, while individuals with depression have a 58% increased risk of developing obesity (Marx et al., 2021).

Consequences of Depression

Depression can significantly impact various aspects of a person's life, affecting their emotional, physical, and social well-being. It is associated with poorer functioning across numerous domains of life including work, home management, social activities, and close relationships (Fried & Nesse, 2014; Hays et al., 1995). Further, depression is often comorbid with other mental health disorders, including anxiety disorders, alcohol abuse or dependence, and drug dependence (Rohde et al., 1991).

The disease burden of depression often goes beyond mental and emotional functioning and quality of life and extends to somatic (physical) health. Over the last three decades, research based on longitudinal studies has illustrated the impact of depression on incident somatic disease development. Meta-analyses have consistently demonstrated that depression increased the risk of overall mortality (RR = 1.81) and the development of many chronic conditions, such as heart disease (RR = 1.81), diabetes (RR = 1.60), hypertension (RR = 1.42), stroke (RR = 1.34) and obesity (RR = 1.58) (Penninx et al., 2013).

Depression can also worsen the outcomes and prognosis of existing medical conditions. For example, depression is associated with negative health behaviors, such as physical inactivity and poor eating habits, which consecutively increase the risk and prognosis of the disease (Bauer et al., 2012). As discussed below, depression might increase the risk of diabetes-related complications among individuals with T2D (Nouwen et al., 2019).

Relationship between Depression and Type 2 diabetes

Depression and Type 2 Diabetes

Comorbidity of diabetes and depression occurs often. Symptoms of depression are more common in the diabetic population as compared to the general population (Anderson et al., 2001). Individuals with T2D have a high (30%) prevalence of depressive symptoms with nearly 11% be affected by major depression (Anderson et al., 2001). A systematic review from the United States (U.S.) and Europe reported that depression was nearly two-fold higher in patients with T2D than in the general population (Bădescu et al., 2016). One U.S. study reported that with a one-point increase in the PHQ-9 depressive symptoms scale there was a 5% increase in the odds of having diabetes (Hunter et al., 2018). Based on such evidence, the *International Diabetes Federation* recommended screening for depressive symptoms in people with diabetes at the initial visit (Sun et al., 2022).

Depression is associated with greater use of health services among adults with T2D, and to higher costs to the health system, compared to the general population, making their co-occurrence a significant contributor to the health system burden (Egede et al., 2016). The use of health services among adults with comorbid T2D and depression might be attributed to managing diabetes and its complications (Molosankwe et al., 2012). Diabetes Canada tracked the out-of-pocket costs for people with T2D and estimated that costs could be as high as \$10,014 per year in some regions of Canada (Diabetes Canada, 2023). Given the high incidence of depression in T2D, the costs of both conditions may represent a considerable burden on Canada's publicly funded healthcare system.

Depression and Risk of Type 2 Diabetes and its Complications

In addition to the high prevalence of depression among adults with T2D, depression has also been associated with a higher risk of incident T2D. Further, most studies reported stronger effects of depression predicting diabetes than for the reverse association (e.g., odd ratios (OR)=1.60 versus OR=1.15) (Mezuk et al., 2008). Various meta-analyses have reported associations between depression and the risk of T2D, ranging from 18% increased risk (Graham et al., 2020) to 60% increased risk (Mezuk et al., 2008). The most recent meta-analysis included 21 studies and combined all measures of depression, such as depressive symptom scales, clinical interviews, physician diagnoses, and use of antidepressants. They reported an 18% increased risk of T2D (RR 1.18, 95% CI 1.12–1.24, I² =45.4%) (Graham et al., 2020).

Although most research on depression and the risk of T2D tends to report combined estimates for both sexes, differences have been noted in a handful of studies reporting sex-stratified results. One U.S. study reported that depressive symptoms were related to increased diabetes risk among women (RR 2.11, 95% CI 1.06- 4.19) but not men (RR 0.67, 95% CI 0.43- 1.10) (Demmer et al., 2015). A 2007 systematic review reported that depression was associated with a 57% increased risk of diabetes in men (n = 6 studies, RR 1.57, 95% CI 1.24-1.99), whereas the risk for women was much lower at 26% (n = 6 studies, RR 1.26 95% CI 0.95-1.67) (Mezuk et al., 2008).

Furthermore, research suggests that depression appears to be present even at various stages of the diabetes continuum. For example, insulin resistance and prediabetes are both important predictors of T2D. A meta-analysis found a small but significant cross-sectional association between depression and insulin resistance (Kan et al., 2013). Depression might also

double the risk of progressing from prediabetes to diabetes over a period of 4.5 years (Deschênes et al., 2016).

Depression among T2D individuals is often associated with poorer adherence to a healthy lifestyle and dietary recommendations, poorer diabetes management, and non-adherence to diabetes medication (Egede & Osborn, 2010; Lunghi et al., 2017; Lustman et al., 2000).

Depression in T2D individuals shows an increased tendency to skip blood glucose self-monitoring (Wagner et al., 2010) and avoid medical appointments (Gonzalez et al., 2008).

An extensive range of medical complications have also been associated with depression (e.g., both microvascular (Hazard Ratios) (HR=1.36) and macrovascular complications (HR=1.25) (Lin et al., 2010). Increased risk of death (HR=1.49) was also widely observed in a meta-analysis of 13 studies (van Dooren et al., 2013). Various prospective studies have indicated that baseline depressive symptoms or disorders are associated with an increased risk of diabetes complications (Wu et al., 2020). Lin et al. (2010) reported that after adjustment for prior complications, depression at baseline was associated with a significant risk of advanced macrovascular (HR=1.24; 95% CI: 1.0-1.54) and microvascular complications (HR=1.36; 95% CI: 1.05-1.75).

Evidence from a recent meta-analysis of longitudinal studies has further confirmed that depression was associated with an increased risk of incident macrovascular (HR=1.38; 95% CI: 1.30–1.47) and microvascular disease (HR=1.33; 95% CI: 1.25–1.41) (Nouwens et al., 2019). Other studies have found, instead, that depression was associated with macrovascular complications but not microvascular complications (Ismail et al., 2017; Wu et al., 2020).

Potential Mechanisms Linking Depression, Type 2 Diabetes, and its Complications

The underlying mechanism explaining the relationship mentioned above might be multifactorial. As presented below, depression can influence the incidence and consequences of diabetes through both behavioral pathways (mechanisms) and biological pathways.

Behavioral Mechanisms

Depression is associated with numerous poor health behaviors, such as frequent fast-food intake and higher sweetened food intake, less involvement in physical activity, and smoking habits (Jacka et al., 2011; Lysy et al., 2008), which can be related to an increase in weight and the risk of T2D (Gray et al., 2015). Depression often leads to poor food choices because those affected tend to prefer a diet high in processed foods, sugar, and refined carbohydrates (Tabák et al., 2014), a similar pattern applies to UPF which often rich in free sugar and refined carbohydrates (Monteiro et al., 2018). There is evidence that choosing these foods can be an attempt to balance neurotransmitters involved in the regulation of mood (Bruinsma & Taren, 1999).

Further, these diets can cause weight gain and greater adipose tissue deposition in the body, which leads to insulin resistance through a series of complex pathways (Kahn & Flier, 2000). Physical inactivity can also accelerate weight gain, affect vascular function, and trigger inflammatory responses in the body (Fischer et al., 2007), all of which could be risk factors for diabetes and its complications. Numerous studies have reported that individuals with depression have been shown to be more sedentary and exercise less than their counterparts (Mutrie, 2003). Findings from a Cochrane review suggested that exercise can be a great tool for reducing depressive symptoms in people with a diagnosis of depression compared with no treatment or control intervention (Cooney et al., 2013).

Besides the diabetogenic processes pictured above, depression might exert its detrimental effects on individuals who already have T2D by prompting risks of diabetes complications. Depression may be related to elements of diabetes self-care, such as compliance with medical treatment, following healthy guidelines, and glucose monitoring at home; individuals with T2D and depression may manage their health condition less vigorously (Rubin & Peyrot, 2002). Researchers have determined that, compared with non-depressed individuals, individuals with depression have a three-fold increase in odds of noncompliance with recommendations related to medical treatment (DiMatteo et al., 2000). Depression is also significantly linked with poorer participation in diabetes education programs (Park et al., 2004).

Further, there is evidence that the relationship between depressive symptoms and the physical symptoms of poor glucose control might be entirely mediated by self-care (McKellar et al., 2004). That said, although these factors likely contribute to the increased incidence of T2D in depression, many studies that adjusted for these lifestyle factors still observed an association between depression and T2D (Frisard et al., 2015; Meng et al., 2018). Furthermore, depression was associated with an increased risk of T2D among individuals with obesity and when adjusting for measures of obesity (Frisard et al., 2015; Meng et al., 2018).

Biological Mechanisms

Depression is linked with dysregulation (impairment) of the hypothalamic-pituitary-adrenal (HPA) axis. This impairment results in the increased release of cortisol-releasing hormone and the subsequently increased secretion of glucocorticoids involved in glucose metabolism (Tabák et al., 2014). Cortisol results in glucose production and increased lipolysis, which simultaneously reduce insulin sensitivity (Tabák et al., 2014). Research has found that depression is linked with increased cortisol concentration (Chan et al., 2003; Mello et al., 2003).

Further, significant sex differences have been reported in the relationship between cortisol and depression; many studies have reported that serum cortisol levels were higher in depressed males than depressed females (Teo et al., 2023). Studies have also reported that depression in females is associated with a blunted cortisol response, while males showed an elevated cortisol response (Fitrikasari et al., 2021). Indeed, it has been postulated that changes in cortisol concentrations may result in obesity, insulin resistance, and T2D (Knol et al., 2006).

Another potential pathway that can play a role in the pathogenesis of these diseases refers to inflammation (Handschin & Spiegelman, 2008). Depression is consistently associated with inflammation as shown in the review of various studies (Xia et al., 2013). Commonly known inflammatory markers are CRP, TNF- α , and IL-1 and IL-6. A meta-analysis reported that adults with depression had higher levels of pro-inflammatory cytokines, notably IL-6, TNF α , and CRP, compared to non-depressed adults (Xia et al., 2013). Further, obesity is also common among depressed individuals and can lead to an increase in inflammatory cytokines and likely contributes to low-grade inflammation (Kanneganti & Dixit, 2012). Systemic inflammation played a critical role in the pathogenesis of T2D and its complications (Yan et al., 2008).

Several other potential factors link depression and T2D. First, it is possible that individuals with depression may have greater contact with the medical system than non-depressed people. Thus, due to higher surveillance, they may be more likely to be detected with T2D (Gim & Shah, 2019; Wilson et al., 2010). Further, increased use of healthcare services is related to more frequent diabetes testing and earlier diagnosis of diabetes (Gim & Shah, 2019; Wilson et al., 2010).

Second, the reverse-causation hypothesis suggests that depressive symptoms may indicate preclinical or undiagnosed T2D (Tabák et al., 2014). However, research has also

reported that the link between depression and incident diabetes remains significant when excluding cases of undiagnosed diabetes (Demakakos et al., 2010). Additionally, the possibility of reverse causation decreases when the association between depression and the long-term incidence of T2D persists (Demakakos et al., 2010; Schmitz et al., 2016).

Third, some antidepressant medications, such as atypical antipsychotics, have been linked with weight gain (Salvi et al., 2017; Tabák et al., 2014), which is a risk factor for the development of T2D. That said, the association between antidepressant use and changes in glucose metabolism is controversial (Azevedo Da Silva et al., 2015). It has been reported that antidepressant use might have short-term glucose-lowering effects (Deuschle, 2013). Some studies (Frisard et al., 2015; Sambamoorthi et al., 2013), although not all (Atlantis et al., 2010), have found an association between depression and T2D even when adjusting for antidepressant use.

Ultra-Processed Foods

Food Processing

Healthy diets are considered a cornerstone lifestyle factor playing an essential role in overall health status. Conversely, unhealthy diets are the leading cause of non-communicable diseases such as CVD and T2D – even more than tobacco, alcohol, and physical activity combined (Lim et al., 2012). There is converging evidence that a healthy diet mainly consists of 'fresh or minimally processed plant-based diet, including fruit, vegetables, pulses, nuts, whole grains, and oily fish (English et al., 2021; Schwingshackl et al., 2017). Such diets, as illustrated by the MDP and DASH, are high in fiber and limit saturated fat, sodium, and added sugar intake. In contrast, unhealthy diets, such as the Western diet, consist of over-refined grains, red and

processed meat, sweets, sugar-sweetened beverages, unhealthy fats, added sugars, and sodium while lacking essential nutrients (Fabiani et al., 2019; Tapsell et al., 2016; Wirfält et al., 2013).

Although specific nutrients and whole food groups in a diet are essential to maintain overall health, researchers have started assessing the other dimensions of diet such as the degree of food processing and its impact on human health (Monteiro et al., 2013). In recent decades, technological advancements have increased ultra-processed foods' availability, affordability, and marketing. It is recognized that “a nutritional transition has resulted in a global shift away from consuming minimally processed foods, and towards ultra-processed alternatives” (Dicken & Batterham, 2021, p. 2; Monteiro et al., 2013).

In parallel, the global prevalence of obesity and related diseases such as T2D has increased in children and adults (Popkin, 2019). In modern society, most of the foods consumed are processed in some sense and in some way; however, these foods differ significantly in the type and purpose of processing. Consequently, judgments of foods simply because they are *processed* are not meaningful. Food processing and its impact on human health can be evaluated when the analysis is (a) discriminating and precise (b) with terms defined and (c) the nature, purpose, extent, and effects of processing is identified and distinguished (Popkin, 2019).

The NOVA Classification

Various classification systems have been developed to classify foods and drinks based on type of processing. Examples include the International Food Information Council, the International Agency for Research on Cancer, and the NOVA classification (a name, not an acronym) (Crino et al., 2017). The NOVA classification is widely used in research and policy (Popkin, 2019). As a food classification system, it is a framework used to categorize foods based on the extent and purpose of food processing. Developed by a team of researchers in Brazil, it

has gained international recognition as a tool for understanding the impact of processing on health and nutrition (Monteiro et al., 2013).

As defined by NOVA, food processing refers to all physical, biological, and chemical modification that occur after foods are separated from their natural form and before they are submitted to culinary preparation (Monteiro et al., 2013). Using this definition, all foods are classified into one of four categories: (a) *unprocessed or minimally processed foods that have* undergone no or minimal processing and are often consumed in their natural state (e.g., fresh fruits and vegetables, nuts, seeds, legumes, whole grains, and fresh or frozen meats); (b) *processed culinary ingredients*, which are substances derived from unprocessed foods, such as oils, butter, sugar, salt, and other substances used to cook and season foods; (c) *processed foods* that have undergone processing (added sugar, salt, oils, or other substances) to make them more durable or palatable (e.g., canned vegetables, fruits in syrup, cured meats, and simple bread and cheese); and (d) *ultra-processed foods* (UPF) prepared mainly or entirely from substances derived from industrial foods with little or no whole food content (e.g., soft drinks, confectionery, savory snacks, many packaged breads, and sweet biscuits) (see Table 1, Monteiro et al., 2019a). This dissertation focuses on the fourth NOVA group, ultra-processed foods (UPF), defined as predominantly industrial formulations.

Table 2.1 Definition of NOVA Classifications (extrapolated from Monteiro et al., 2019a)

Group	Definition	Examples
1. Unprocessed and minimally processed foods	Unprocessed foods altered by processes such as the removal of inedible or unwanted parts, drying, crushing, grinding, fractioning, roasting, boiling, pasteurisation, refrigeration, freezing, placement in containers, vacuum packaging, or non-alcoholic fermentation. Salt, sugar, oils or fats, or other food substances are not added. The primary aim is to extend the life of the food, enabling storage for longer use, and to make preparation easier or more diverse.	Fresh, squeezed, chilled, frozen, or dried fruit, leafy and root vegetables, brown rice, white rice, corn cob, beans, lentils, chickpeas, potatoes, sweet potatoes, mushrooms, meat, poultry, fish, seafood, meat cuts, eggs, fresh or pasteurised milk or plain yoghurt, fresh or pasteurised fruit or vegetable juices (with no added sugar, sweeteners or flavours), grits, flakes or flour made from corn, wheat, oats, or cassava, nuts and other oily seeds (with no added salt or sugar), herbs and spices used in culinary preparations, such as thyme, oregano and pepper, tea, coffee, and water.
2. Processed culinary ingredients	Substances derived from unprocessed and minimally processed foods, or from nature. They are created by industrial processes including pressing, centrifuging, refining, extracting, or mining, and used in the preparation, seasoning, and cooking of group 1 foods.	Oils and fats, sugar, and salt.
3. Processed foods	Industrial products made by adding processed culinary ingredients found in group 2 to group 1 foods, using preservation methods such as canning and bottling. For breads and cheeses, non-alcoholic fermentation is used. Food processing in group 3 aims to increase the durability of group 1 foods and make them more enjoyable, by modifying or enhancing their sensory qualities.	Canned or bottled vegetables and legumes in brine, salted or sugared nuts and seeds, salted, dried, cured, or smoked meats and fish, canned fish (with or without added preservatives), fruits in syrup (with or without added antioxidants), freshly made unpackaged breads and cheeses.
4. Ultra-processed foods	Formulations of ingredients, mostly of exclusive industrial use, resulting from a series of industrial processes, many requiring sophisticated equipment and technology. Processes enabling the manufacture of ultra-processed foods include the fractioning of whole foods into substances, chemical modifications of these substances, assembly of unmodified and modified food substances using industrial techniques such as extrusion, moulding and pre-frying, frequent application of additives whose function is to make the final product palatable or hyper-palatable ('cosmetic additives'), and sophisticated packaging, usually with synthetic materials.	Carbonated soft drinks, sweet or savoury packaged snacks, chocolate, confectionery, ice cream, mass-produced packaged breads and buns, margarines, biscuits, pastries, cakes, breakfast 'cereals', pre-prepared pies and pasta and pizza dishes, poultry or fish nuggets, sausages, burgers, hot dogs and other reconstituted meat products, powdered and packaged 'instant' soups, noodles and desserts.

UPF, which are a hallmark of Western diets, contain a higher content of total fats, saturated fats, added sugar, energy density, and salt (Monteiro et al., 2018). UPF have become a significant, and in some cases, the primary source of dietary energy in high-income countries, including the U.S. and Canada. Their sales and consumption are gradually increasing in lower-middle- and middle-income countries. In Canada, 48% of all daily energy intake comes from UPF (Moubarac et al., 2017). Further, results based on the national dietary surveys from Canada show dose-response (i.e., ways people are affected by different levels of exposure) associations between the dietary share of UPF (i.e., % of total daily energy) and excessive intakes of free sugars, saturated fats, and sodium, and a lower intake of fiber (Monteiro et al., 2019a ; Moubarac et al., 2017). Moreover, the more UPF consumed, the less fresh and minimally processed foods are consumed (including fruits, vegetables, and legumes) (Moubarac et al., 2017).

UPF consumption is also inversely associated with the socioeconomic position in high-income countries (Moubarac et al., 2013) with the opposite being true in middle-income countries (Simões et al., 2018). A randomized controlled trial showed that a diet high in UPF could significantly increase energy intake and weight gain over two weeks compared with non-ultra-processed food (Hall et al., 2019).

However, the impact of UPF goes beyond their impact on body weight; mounting evidence from systematic reviews and meta-analyses of prospective cohort studies and cross-sectional studies has suggested that high UPF consumption is linked with an elevated risk of several chronic conditions (Chen et al., 2020; Elizabeth et al., 2020). Many nations, such as Canada, Brazil, Uruguay, Ecuador, and Peru, have recognized the consequence of food processing (as mentioned above and discussed below), particularly UPF, and recommend avoiding the consumption of these foods and drinks (Monteiro et al., 2018).

Ultra-processed foods and Risk of Type 2 Diabetes/Complications

Diets high in UPF consumption are associated with the higher glycemic loads (Moubarac et al., 2017). Diets high in glycemic load induce hyperglycemia (i.e., excessive glucose in blood plasma), which is associated with increased pro-inflammatory cytokines, including IL-6 and TNF- α , subsequently leading to insulin resistance by disruptions in insulin signaling (Kim et al., 2018). Evidence from a prospective study showed that a UPF consumption is linked to an increased risk of chronic inflammation (Lopes et al., 2019) and predict is a predictor of T2D independently of BMI and other diabetes risk factors (Delpino et al., 2022).

To continue, a recent meta-analysis assessed studies where UPF were classified according to the NOVA food classification system and showed that high UPF consumption increased the risk of T2D by 48% compared with low consumption (RR: 1.48; 95% CI: 1.16–1.89) (Delpino et al., 2022). Further, when results were stratified by sex, they were significant in men and women. And high UPF intake increased the risk of diabetes by 37% in men (RR: 1.37; 95% CI: 1.23–1.53) compared to 25% in women (RR: 1.25; 95% CI: 1.12–1.39) (Delpino et al., 2022). Using data from the 2015 *Canadian Community Health Survey (CCHS–Nutrition)*, Nardocci et al (2021) found that adults in the highest tertile of UPF consumption had 37% higher odds of diabetes compared with those in the lowest tertile.

Among individuals with T2D, UPF consumption might increase the risk of developing complications related to T2D. Advanced glycation end products (AGEs), or mycotoxins, are a heterogeneous group of compounds associated with oxidative stress and chronic inflammation (Goldin et al., 2006). AGEs can result in oxidative stress in various cells, activating inflammatory signaling cascades and, consequently, play a crucial role in the pathogenesis of diabetes complications (Yan et al., 2008). Because of high-fat content and being subject to high

heat during cooking or processing (e.g., high-heat processed grain products and red meat), UPF tend to be high in AGEs. A recent study found that, in individuals with T2D, high consumption of processed foods was associated with poor glycemic control and a greater likelihood of microvascular complications (Nicolau et al., 2020).

Ultra-processed food and Depression

Previous studies have focused on depression and unhealthy diet such as UPF as independent risk factors of T2D and its complications. However, depression and diet do not appear independent with evidence showing a bidirectional relationship between them (Beydoun et al., 2016). According to the APA (1980), a decrease or increase in appetite is also a symptom of depression. This indicates a possible link between depression and (unhealthy) diet (APA, 1980). Still, it remains uncertain whether depressive symptoms lead to the consumption of an unhealthy diet or if the consumption of an unhealthy diet leads to greater severity of depression.

Research shows that greater depression severity is associated with unhealthy diet quality, as measured by the AHEI (Appelhans et al., 2012). Other studies have also found associations between greater depressive symptoms and lower fruit and vegetable consumption (Payne et al., 2012), frequent fast-food intake (Crawford et al., 2011) and higher sweetened food consumption (Jeffery et al., 2009). Further evidence suggests that a healthy dietary pattern, such as the MDP, is associated with a lower risk of depression (Skarupski et al., 2013). Lai et al.'s (2014). Comprehensive systematic review and meta-analysis found that a healthy dietary pattern was significantly associated with a reduced risk of depression (OR: 0.84; 95% CI: 0.76, 0.92).

A study conducted on middle-aged Mediterranean population showed that participants with high UPF consumption had a 31% higher risk of developing depression during follow-up than those with the lowest consumption (Gómez-Donoso et al., 2020). A recent meta-analysis

also showed that higher UPF consumption was associated with a 28% increased risk of depressive symptoms (RR = 1.28; 95% CI: 1.19 -1.38) (Mazloomi et al., 2022). Further, a dose-response analysis demonstrated a positive linear correlation in that for every 10% increase in UPF consumption, an 11% higher risk of depression was observed (Mazloomi et al., 2022).

Research and Knowledge Gap

As discussed, diverse plausible mechanisms have been suggested for the association between depression and T2D. One mechanism by which depression might affect diabetes risk is through increasing health-risk behaviors (Tabák et al., 2014). A meta-analysis of longitudinal studies examining depression as a risk factor for diabetes found that adjustment in BMI and lifestyle factors (mainly physical activity) lowered the risk of T2D in people with depression. This result suggests that higher BMI and physical inactivity might contribute to this association (Rotella & Mannucci, 2013).

However, fewer studies have directly mapped the relationship between unhealthy diets, such as UPF consumption, depression, and T2D incidence (the focus of this study). A French population-based study examined the extent to which lifestyle factors, mainly diet and physical activity, added to the relationship between depression and metabolic syndrome. A path analysis showed that 23% of the association between these variables was explained by diet and physical activity (Matta et al., 2019). Prior studies that focused on depression and an ultra-processed diet as independent predictors of T2D concluded that both may exacerbate a common pathway thereby resulting in a substantially elevated risk for T2D and its complication (Schulze et al., 2005; Yu et al., 2015).

Various studies have observed direct and indirect links between an ultra-processed diet, obesity, inflammation, depression, and T2D (Dandona et al., 2004; Matta et al., 2019; Oddy et

al., 2018). Nevertheless, despite evidence that depression and UPF consumption are separately linked with T2D, little is known about how the combination of these modifiable factors increases T2D and its complications risks. In addition, despite evidence showing that depression can influence behavioral factors (e.g., smoking, alcohol and drug consumption, and dietary habits) and then can increase the risk of T2D, there is little information on how much depression can influence UPF consumption and then subsequently influence T2D incidence – in another words, how (if) UPF consumption meditates the association between depression and T2D.

To address this research and knowledge gap, this dissertation seeks to investigate the relationship of T2D with UPF consumption and depressive symptoms. This inaugural line of thought and investigation strives to bring new knowledge and insight to bear on this phenomenon.

Manuscript-Based Dissertation

Chapters 3, 4, and 5 each contain a standalone manuscript pertaining to different facets of this study (three research objectives). Each manuscript fully recounts the methods employed to sample, collect, and analyze data pursuant to the three research objectives. All three studies (chapters) used baseline data from the CARTaGENE study-Phase A. CARTaGENE is the public research platform of the Centre hospitalier universitaire (CHU) Sainte-Justine (affiliated with the Université de Montréal) that aims to accelerate health research. It investigates modifiable environmental and lifestyle factors and the genomic determinants of chronic diseases (Awadalla et al., 2013) (see <https://cartagene.qc.ca/>).

CARTaGENE is a population-based cohort meaning people are not recruited for any particular disease. Instead, they represent a random selection from among the general population. CARTaGENE comprises both biological samples (biobank) and data on the health and lifestyle

of 43,000 Quebec men and women aged 40 and 69 (most at risk of contracting chronic diseases) living in one of six metropolitan areas at recruitment (Awadalla et al., 2013). Herein, CARTaGENE data were combined with administrative data from the governmental provincial health insurance database, the Régie de l'Assurance Maladie du Québec (RAMQ).

The transition from one study (manuscript, chapter) to the next is prefaced with a *Bridging Statement*. Chapter three (Cox regression models) recounts a prospective community study that dealt with the role of UPF consumption and depressive symptoms on T2D incidence. This manuscript has been published at *Public Health Nutrition* (2022). Chapter four (Cox regression models) assessed the association between depressive symptoms, UPF consumption, and the *risk of developing* diabetes-specific complications in adults with T2D. This manuscript is currently under review at *Frontiers in Endocrinology*. Chapter five (logistic regression and mediation analysis) focused on the mediating role of UPF consumption in the association between depression and T2D incidence. This manuscript is in progress intended for peer review.

Chapter 3: Manuscript 1. The role of ultra-processed food consumption and depression on type 2 diabetes incidence: A prospective community study in Quebec, Canada

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Abstract

Objectives: The goal of the present study was to evaluate the association between depression and ultra-processed food (UPF) consumption as risk factors for developing type 2 diabetes (T2D).

Design: A prospective community study.

Setting: Baseline data (2009–2010) from CARTaGENE community health study from Quebec, Canada, were used. Food and drink consumption was assessed using the Canadian-Diet History Questionnaire II and grouped according to their degree of processing by the NOVA classification, and participants were categorised into tertiles of UPF (g/d). Depression was defined using either a validated cut-off score on the Patient Health Questionnaire-9 or antidepressant use. The outcome was the incidence of T2D, examined in 3880 participants by linking survey data with administrative health insurance data. Cox regression models estimated the associations between UPF, depression and incident T2D.

Participants: 40–69-year-old individuals at baseline.

Results: In total, 263 (6·8 %) individuals developed T2D. Participants with high depressive symptoms and high UPF consumption showed the highest risk for T2D (adjusted hazard ratios (aHR) = 1·58, 95 % CI (0·98, 2·68)), compared to those with low depressive symptoms and low UPF consumption. The risk for T2D was similar when high depressive symptoms and antidepressant use were combined with high UPF (aHR 1·62, 95 % CI (1·02, 2·57)).

Conclusions: This study shows that co-occurring depression and high UPF consumption were associated with a higher risk for T2D. Early management and monitoring of both risk factors might be essential for diabetes prevention.

Keywords: Ultra-processed food, Depression, CARTaGENE, Type 2 diabetes.

Introduction

Type 2 diabetes (T2D) is a worldwide, increasingly prevalent chronic disease that can lead to adverse outcomes, such as microvascular and macrovascular complications, disability, and early mortality (1).

Mental health problems, such as depression, are well-established comorbidities of T2D (2). Evidence from meta-analyses has shown that depression increases the risk for T2D incidence by 40–60 % (3). The underlying mechanisms explaining this relationship might be multifactorial; it is likely that depression may influence the incidence and consequences of diabetes through behavioural and biological pathways. For example, several lifestyle-related behaviours, such as poor dietary habits and decreased physical activity, can contribute to this relationship (4,5). Therefore, health behaviours are important factors for diabetes risk.

Healthy diets, among other factors such as physical activity, are potentially modifiable factors that can help prevent and manage T2D (6). A meta-analysis of prospective studies found that healthy dietary patterns or healthy diet indexes, such as the Mediterranean, the Dietary Approaches to Stop Hypertension, the Healthy Eating Index and the Alternative Healthy Eating Index, are associated with a lower risk for T2D (7).

The modern food system is facing a considerable challenge due to the rapid increase in the availability and consumption of ultra-processed foods (UPF) and drinks (8). UPF are defined as formulations of industrial ingredients that result from a series of industrial processes (hence ‘ultra-processed’). They typically are of low nutritional quality and contain little or no whole foods, are ready-to-consume or heat up and are fatty, salty or sugary and depleted in dietary fibre, protein, various micronutrients and other bioactive compounds (8). Recent studies from high-income countries, including Canada, suggest that UPF account for 50–60 % of the total

daily energy intake (9-11). Higher consumption of UPF was associated with a 31 % increased risk of obesity, a 37 % increased risk of diabetes and a 60 % increased risk of hypertension (12).

Although depression and UPF consumption have independently been shown to increase the risk for T2D (4,12), the extent to which the combination of these factors increases the risk for T2D has yet to be investigated. For example, depressive symptoms are associated with high levels of inflammatory markers such as C-reactive protein, TNF- α , IL-1 and IL-6 levels, which are associated with T2D (13). Further, UPF are also associated with these inflammatory markers (14) and are also associated with T2D incidence (12). Therefore, it is possible that depression and UPF consumption may exacerbate a common pathway, resulting in a substantially elevated risk for T2D incidence. Hence, it is particularly relevant to increase our understanding of the relationship between UPF consumption, depression, and the risk of T2D.

Thus, the goal of this study was to prospectively investigate the potential additive interaction between UPF consumption and depression on the incidence of T2D in a Canadian community sample. We hypothesised that individuals with both high depression and high UPF consumption at baseline would have a higher risk of developing T2D than those with high depression only and with high UPF consumption only or neither.

Methods

Study population

Baseline data used in this study were from the CARTaGENE (<https://cartagene.qc.ca>) cohort study (2009–2010), a community health survey conducted in the Canadian province of Quebec in the adult population aged 40–69 years living in metropolitan areas (Montreal, Quebec City, Sherbrooke and Saguenay) (15). CARTaGENE participants were randomly recruited from the governmental provincial health insurance database, the Régie de l'Assurance Maladie du

Québec (RAMQ). Under this government health insurance plan, most residents of Quebec have health coverage (15). Recruitment, enrolment and data collection methods are described in detail elsewhere (15). All participants provided informed consent to participate in the CARTaGENE cohort study and agreed to have their data linked with the provincial health insurance database. Participants provided information on demographic, health characteristics and biospecimens for clinical measures during their interviews (15). Additionally, a nutrition component was added to a subset of the participants (15). This component includes a questionnaire relating to eating habits (described below). Follow-up data referring to T2D incidence were obtained by linking participants with diagnostic codes from the RAMQ database.

Measures

Depressive symptoms

Depressive symptoms were measured using the Patient Health Questionnaire-9, which consists of nine questions related to vegetative, emotional, behavioural and cognitive symptoms during the past 2 weeks (16). Responses ranged from ‘not at all’ (0) to ‘every day’ (3), with a summary score ranging from 0 to 27. Depressive symptoms were defined as having a Patient Health Questionnaire-9 summary score of 6 and higher, which includes moderate to severe depressive symptoms. In this study, a score of 6 or higher is categorised as ‘high depressive symptoms’. This cut-off score has shown good performance and has been used in many studies, including CARTaGENE cohort (17,18). When compared with the fully structured interviews for major depressive disorder, the Patient Health Questionnaire-9 cut-off of 6 has a sensitivity of 0.91 and a specificity of 0.61(19).

Antidepressant use

Participants brought their current medication or reported their current medication at the baseline interview. Medication was classified as an antidepressant based on the medication name (20).

Dietary intake assessment

Dietary intake in the CARTaGENE survey was measured using the Canadian-adapted Diet History Questionnaire II (C-DHQ II) (21). C-DHQ II is a food frequency questionnaire (FFQ) initially developed by the US National Cancer Institute and modified to reflect food availability, brand names, nutrition composition and food fortification in Canada (22). It contains 164 questions related to food, portion size, frequency and vitamin/mineral supplement use during the last 12 months.

A commonly used unit or portion size is specified for most food items. Daily consumption of each FFQ food item was computed based on one of four units of time, depending on which answer choice was selected: year, month, week or day. For this study, all the items used for the analysis were using 'all year' format, which implies that items using daily consumption for summer, not in summer, winter, not in winter, in season and out of season format were not included in the present study (21,23).

Daily consumption of the items was converted into daily equivalents such as never = 0; 1–6/year = 0.01; 7–11/year = 0.02; 1/month = 0.03; 2–3/month = 0.07; 1/week = 0.14; 2/week = 0.29; 3–4/week = 0.48; 5–6/week = 0.74; 1/day = 1; 2 or more = 3 as specified by the C-DHQII database (23). Secondly, portions of consumed food items were converted into grams by using the nutrient database for the C-DHQII (24). Portions are sex-specific and based on the percentiles of intake reported in the Canadian Community Health Survey – Cycle 2.2 Nutrition (22). Then, the consumed amount for every food item was calculated by multiplying the

frequency per day and grams of consumption. In the present analysis, food items without portion size and items such as vitamins, minerals or herbal supplements were excluded.

Similar to any lengthy and self-administered questionnaire, FFQ is often associated with non-responses. Food items on an FFQ might be omitted for different reasons, for example, the food may not be consumed by respondents, or they might have difficulties remembering the frequency and amount of intake (25,26). Therefore, zero imputation was used to deal with missing data in FFQ based on the assumption that items which were left blank in the data were not consumed by the respondent (26).

Food and beverage items of FFQ were categorised according to NOVA (not an acronym) food groups – a classification system which considered all physical, biological and chemical modification that occurs to foods after they are separated from their natural form (8). As a result, all foods are classified into one of four groups. NOVA group 1 includes unprocessed or minimally processed foods, meaning foods processed in a way that does not add or introduce a substance to the original food. However, these foods might involve processing with the aim of extending the shelf-life of unprocessed foods, allowing their storage for longer use and facilitating or diversifying food preparation. Fruit and vegetables, grains (cereals), fresh and pasteurised milk products and meat and fish are some examples of NOVA group 1. NOVA group 2 comprises processed culinary ingredients such as salt, sugar, vegetable oil and butter. These products are extracted and refined from NOVA group 1 food or obtained from nature. Pressing, refining, grinding, mining and spray drying are the methods involved in obtaining these products. NOVA group 3 contains processed foods to which salt, sugar or other substances of culinary use, such as oil or vinegar, have been added, and methods involving smoking, curing or fermentation have been performed to preserve them or to enhance their palatability. Food products in this

group are canned or bottled food items such as vegetables and fruits, cheeses and freshly made bread. NOVA group 4 comprises UPF and drinks that were prepared mostly or entirely from substances derived from industrial foods, with little or no whole food content. Ingredients present in these foods are modified starches, hydrogenated oils, protein isolates and additives whose purpose is to increase the shelf life, hyper-palatable, protect original properties and prevent the proliferation of micro-organisms. Examples of products are ready-to-eat meals, carbonated drinks, biscuits, processed meat, and sugared milk and fruit drinks (8). Food and beverage items that were defined in the fourth category of the NOVA classification for the present study were identified and verified by the two researchers, and these UPF items were also classified in group 4 in the other cohorts, such as Nurses' Health Studies, The Health Professionals Follow-up Study and Growing Up Today Studies (27).

To estimate UPF consumption (g/d), we summed the amount consumed (g/d) of each food and beverage item classified in the fourth category of the NOVA classification (a total of thirty foods and seven beverage items). Participants were then divided into tertiles according to the total consumption of UPF (g/d). Low and middle tertiles were considered as one group for joint association analysis.

Incidence of type 2 diabetes mellitus

The primary outcome was the incidence of diabetes. This was assessed using diagnostic codes in RAMQ billing database. Diagnostic codes were based on the World Health Organization's International Classification of Diseases, 9th, or 10th edition (ICD-9 and ICD-10, respectively), and the code was ICD-9 code 250 and ICD-10 code E11. Participants were followed for a maximum of 7 years using administrative data from the date of their CARTaGENE baseline assessment. The date of the first diagnosis or hospital admission for

diabetes was recorded. Observational time was calculated from the day of baseline assessment to the day of T2D onset, the date of death or the study end date of 31 December 2016.

Covariates

Several factors might affect the association between depression, UPF consumption and T2D incidence. We, therefore, included the following covariates in our analyses: age, sex, self-reported ethnicity (white and other), marital status, education, annual household income and country of birth (born in Canada or outside) and smoking status ('currently smokes daily or occasionally', 'past smoker' or has 'never smoked'). Alcohol consumption was defined as whether participants consumed alcohol daily or not. Physical activity was measured by asking participants 'how many days in the last week they engaged in moderate/vigorous activity'. High physical activity was defined as 5 or more days with moderate activity or 3 or more days with vigorous activity in the past week.

Statistical analysis

Inclusion criteria

Only participants with information on the nutrition component at baseline were included (n 7011). Implausible reporting, particularly under-reporting, is a widely recognised limitation of dietary assessment methods; participants tend to underestimate their total energy intakes and under-report intakes of foods that are deemed unhealthy or socially undesirable, such as foods that are high in fat and refined carbohydrates. Therefore, we excluded all participants using the simpler recommended method (excluding implausible energy intakes below 800 kcal/d or above 4000 kcal/d in men and below 500 kcal/d or above 3500 kcal/d in women (n 1240)). This approach has been used in previous studies (28). There were more under-reporter (n 992) than over-reporter (n 248) in our sample. Further, those participants who reported diabetes at baseline

based on a positive response to the following question: ‘Has a doctor ever told you that you had diabetes?’ (n 326) and those whose data could not be linked to the provincial health insurance database (n 3) were also excluded. In addition, participants whose response rates were less than 50 % on the UPF items (n 1562) were excluded. A total of 3880 participants were included in the final analyses (Fig. 1). Moreover, we performed two sensitivity analyses first with a) a 40 % response rate on UPF items (sample size n 4364) and b) a 60 % response rate on the UPF items (sample size n 3012) to test the robustness of the study (online supplementary data).

Cox proportional hazards regression models were first conducted to examine the individual association of UPF consumption, depression symptoms and antidepressant use on the incident T2D. To evaluate a potential additive interaction between UPF and depressive symptoms, we defined four groups: (a) lower/middle tertile of UPF consumption and low depressive symptoms (LUND as the reference group); (b) lower/middle tertile of UPF consumption and high depressive symptoms (LUD); (c) higher tertile of UPF consumption and low depressive symptoms (HUND) and (d) higher tertile of UPF consumption and high depressive symptoms (HUD). Cox regression was conducted to evaluate a potential additive interaction of depressive symptoms and UPF on T2D incidence. Finally, an additional analysis was performed by combining depressive symptoms with antidepressant medications as an indicator of depression. Four groups were created: (a) lower and middle tertile of UPF consumption and low depressive symptoms and no antidepressant use (LUNDA as the reference group); (b) lower and middle tertile of UPF consumption and high depressive symptoms or antidepressant use (LUDA); (c) higher tertile of UPF consumption and low depressive symptoms and no antidepressant use (HUNDA) and (d) higher tertile of UPF consumption and high depressive symptoms or antidepressant use (HUDA).

All the Cox regression analyses were performed in unadjusted models, in models adjusted for age and sex only and in fully adjusted models. Hazard ratios (HR) with 95 % CI are reported. Missing information on the covariates was imputed using the fully conditional specification with discriminant or logistic methods using PROC MI procedure SAS. To examine the interaction between depression and UPF consumption on the risk of T2D development, the RERI (relative excess rate due to interaction) index was computed (29). RERI is an index for an interaction on the additive scale and was calculated using the following equation: $RERI = HR_{AB} - HR_A - HR_B + 1$ (29), where HR_{AB} is the presence of both elevated depression and UPF consumption, HR_A is the presence of depression only and HR_B is the presence of UPF consumption only. A RERI greater than zero indicates a more than additive (synergistic) interaction (29).

Results

The main food groups contributors to UPF intake are shown in Table 4.1. Overall mean consumption of the UPF was 225.8 g/d (s.d. 331.8), and mean consumption in the lower, middle and highest tertile was 107.1 (s.d. 33.9), 209.1 (s.d. 33.4) and 579.5 g/d (s.d. 407.0), respectively. Soft and isotonic drinks, fast food and ready to eat and cookies, biscuits, muffins and cake food groups were the main food groups contributing to the total of UPF. Sample characteristics are presented in Table 4.2. At baseline, the sample was on average 54.2 years old (s.d. = 7.5). There were 2327 (60 %) participants in the LUND group (reference group); 260 (6.7 %) participants in the LUD group; 1114 (28.7 %) participants in the HUND group and 179 (4.6 %) participants in the HUD group. Participants in the HUD group had a higher mean intake of UPF: 605 (711.5) g/d. Compared with participants in the other groups, they were more likely to be smokers, physically inactive and have a lower proportion of post-

secondary education. A total of 263 (6.8 %) individuals developed T2D during the observation period. T2D incidence was 5.9, 6.9, 8.2 and 8.9 % for LUND, LUD, HUND and HUD, respectively.

When compared with the complete baseline CARTaGENE sample (without diabetes), our sample included a greater proportion of females (59.9 % compared with 47.6 % of the overall baseline population) and a greater proportion of participants in the middle-income level compared to the baseline sample (60.8 and 50.3 %, respectively).

Table 4.3 describes the results of three univariate Cox regression analyses. Participants in the highest tertile of UPF consumption had the highest risk for T2D incidence in the fully adjusted model (HR = 1.47, 95 % CI (1.07, 2.03)) as compared to those with the lowest UPF consumption. The HR for depressive symptoms (Patient Health Questionnaire-9 $\geq$ 6) was 1.12 (95 % CI (0.85, 1.76)) when adjusted for all the covariates. Similarly, HR for antidepressant use was 1.31 (95 % CI (0.85, 2.01)) in the fully adjusted model.

Table 4.4 presents the results from the additive interaction analysis, and the reference category in model 1 was the LUND group. Participants in the HUD group had the highest risk of T2D: the HR was 1.58 (95 % CI (0.93, 2.68)) in models adjusted for all the covariates. Those in the HUND group had a higher risk for T2D compared with those in the LUD group. The RERI coefficient was 0.26 (95 % CI (-0.32, 1.45)) in the adjusted model, suggesting a more than additive interaction. However, the CI is wide and includes 0. We found a similar risk in model 2 when combining depressive symptoms and antidepressant medication as indicators for depression. The highest risk for T2D was found in the HUDA group in the model adjusted for age and sex (HR 1.78, 95 % CI (1.13, 2.81)) and in the model adjusted for all the covariates (HR 1.55, 95 % CI (1.01, 2.37)). The RERI was 0.09 (95 % CI (-0.81, 1.23)) in the adjusted model.

Our sensitivity analyses showed similar results, suggesting that participants with both conditions, depression and UPF consumption, were at higher risk for developing diabetes than their counterparts (online supplementary Data).

Discussion

In this prospective community study of 3880 individuals aged 40–69 years without T2D at baseline, we evaluated the impact of depression and UPF consumption on T2D incidence over approximately 7 years. The results suggest an interaction between depression and UPF consumption in relation to an increased risk of T2D. Cox regression analyses indicated that participants with both elevated depression and high UPF consumption at baseline were at an increased risk of developing T2D compared to those with high depression only and those with high UPF consumption only or neither.

To our knowledge, no prior study evaluated the interaction of UPF consumption and depressive symptoms on T2D incidence. Previous studies have looked at interactions between depression and metabolic factors on T2D incidence. One study has reported that the interaction between depression and obesity was more strongly associated with the risk of T2D than the sum of the individual effect (30). Further, a similar finding was seen in Midlife Development Study in the USA, where interactions were found between central obesity and depression on T2D incidence (adjusted risk ratios = 2·16, 95 % CI (1·18, 3·98)) (31).

A Canadian study found that the combined effect of depressive symptoms and metabolic dysregulation increased the risk of T2D over a 4-year follow-up period (adjusted OR = 6·61, 95 % CI (4·86, 9·01)) (17). A cross-sectional study from Australia (13 763 men aged 18–55 years) showed that men having both comorbid depression and obesity had a 7·6 (OR) times higher risk of T2D compared to men without comorbid depression and obesity (32).

There are several pathways in which depression or depressive symptoms may be associated with an increased risk of developing T2D. Health-risk behaviours might have a key role in this association (3). A meta-analysis of longitudinal studies examining depression as a risk factor for diabetes found that adjustment in BMI and lifestyle factors (mainly physical activity) lowered the risk of T2D in people with depression, suggesting that higher BMI and physical inactivity might contribute to the association discussed above (2). Healthy behaviours, including good eating behaviours, are significant lifestyle factors that can lower the risk of T2D. Depression has been shown to adversely impact these behaviours (2,3), which might affect the management of T2D. Depression is associated with increased caloric consumption and less involvement in physical activity (33,34), which can be related to an increase in weight and an increase in T2D risk (35).

Higher consumption of UPF and depressive symptoms share common biological mechanisms, and the co-occurrence of both conditions might intensify the risk of developing T2D. First, activation of the hypothalamic–pituitary–adrenocortical (HPA) axis and the autonomic nervous system might play a key role. Unstable cortisol concentrations are linked with depression, obesity, insulin resistance and T2D (3). Depressive symptoms and T2D are linked with the hypothalamic–pituitary–adrenocortical axis in disease development. Obesity, which is linked with higher consumption of UPF (12), is a well-established risk factor development of T2D (12). Further, a high concentration of inflammatory markers may be involved in developing T2D in individuals with depression (13). Studies have reported that both depressive symptoms and UPF or western-style dietary patterns are associated with inflammatory markers such as C-reactive protein, TNF- α , IL-1 and IL-6 levels (13,14).

Additionally, diets high in sugar, commonly found in UPF (36), might be a potential mechanism mediating the relationship between depressive symptoms and T2D. High sugar consumption can activate brain regions associated with the reward response and provoke a more intense feeling of hunger than in low-sugar diets (37). These reward responses can drive the loss of self-control, overeating and subsequent weight gain, leading to the development of T2D (37,38). Furthermore, consuming sweet foods and added sugar has also been linked to depression (39).

Some antidepressant medications might act as mediators of this relationship since antidepressant use seems to be associated with long-term weight gain (for some antidepressants) and may represent a key biological factor for the development of T2D (13, 40). Higher UPF consumptions and depressive symptoms might stimulate each other's occurrence, which can, in turn, result in obesity, inflammation and insulin resistance. Therefore, it is possible that it can lead to a vicious cycle that further increases the risk of depression and T2D.

Furthermore, beyond the unhealthy nutritional composition of UPF, these foods are also impacting health in different pathways. Recent concern has emerged about the manufacturing and packaging process of UPF. Studies have linked the cosmetic additives commonly used in UPF, such as flavours, emulsifiers and thickeners, to gut dysbiosis and may initiate inflammation in the gut (41). Besides these, contamination from food packaging (e.g. phthalates, bisphenol A) is linked to adverse health effects (42,43). However, more research is needed to understand the mechanisms of action and the relative effects of UPF on health.

Strength and limitation

This study utilised a sample of individuals with no diabetes at baseline and up to 7 years of follow-up data. This study combined survey and administrative data to evaluate the association of UPF and depressive symptoms on T2D incidence in middle-aged individuals. We

used two different measures of depression, and the robustness of the study findings was assessed using two different response rates of UPF consumption in a sensitivity analysis.

Our work also has several limitations. Data on diabetes at baseline were based on self-reports and not on clinical measures. Although diabetes surveillance systems in Canada use at least one hospitalisation record or at least two physician claims in a 2-year period, we choose the single claim to diagnose the diabetes cases because of our limited follow-up time. Depressive symptoms were assessed at baseline only. The Patient Health Questionnaire-9 is a self-report scale that measures depressive symptoms experienced in the past 2 weeks and does not account for the history and treatment of depression. Given that depressive symptoms were not measured during the follow-up, symptoms may vary and change over time.

Similarly, dietary intake data measured using C-DHQ II at baseline were assessed by self-report, which may be subjected to reporting bias. Further, dietary intake data were only available at one point in time; therefore, it might be possible that participants change their intake of UPF during the follow-up. Thus, a potential effect of diet quality change over time cannot be established. Participants of the CARTaGENE study were volunteers in a nutrition component and thus are more interested in nutritional issues and healthy lifestyles than the general population. Their consumption of UPF may be lower compared to the general population, which may underestimate the risk investigated in our study. The C-DHQ II was not specifically designed to collect data about the new NOVA classification of UPF consumption. CARTaGENE participants were also limited to mostly white participants and metropolitan; thus, generalisation to other ethnic groups and rural areas cannot be established (16).

Conclusion

In conclusion, in this large-scale longitudinal study combining survey and administrative data, we evaluated the combined effect of UPF consumption and depression on the incidence of T2D in individuals aged 40–69 years, with up to 7 years of follow-up. This research highlights the interaction between UPF consumption and depressive symptoms as potentially modifiable risk factors for T2D. Given the unprecedented rates of diabetes worldwide, the scientific community needs to do more to understand the risk factors of T2D, and interaction between risk factors may be one approach. In clinical practice, early management and monitoring of both risk factors might be an important step in the diabetes prevention strategy.

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Conflicts of interest: There are no conflicts of interest.

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Table 3.1 Contribution of each food group to total amount of ultra-processed foods consumed in the CARTaGENE study cohort (n=3880)

Food groups (n= 37)	Contribution to total ultra-processed foods intake (%) *	Daily amount consumed mean g/d (SD)
<i>Beverages (n=7)</i>		
Dairy beverages	5.3	11.8 (38.3)
Soft/isotonic drinks	44.0	99.3 (294.6)
Fruit drinks	4.5	10.2 (87.4)
<i>Solid Foods (30)</i>		
Processed meat	4.5	10.2 (15.2)
Fast food and ready to eat	11.2	25.4 (27.9)
Breakfast cereals	4.5	10.1 (14.5)
Cookies, biscuits, muffins, and cake	11.7	26.5 (37.7)
Potato chips and salty snacks	3.4	7.6 (10.5)
Confectionery and chocolate	2.8	6.3 (15.3)
Ketchup, salad dressing and similar	4.5	10.2 (12.3)
Ice-cream	2.3	5.2 (10.6)
Jelly and jams products	1.4	3.1 (6.1)
Total	100	225.8 (331.8)

*Contribution (%) of each food group/beverage to the total consumption of ultra-processed food was calculated by dividing the amount (g/d) of each food group by the total amount of ultra-processed foods (g/d) multiplied by 100.

Table 3.2 Baseline characteristics of the study sample

	LUND (n = 2327)	LUD (n = 260)	HUND (n =1114)	HUD (n =179)	Total (n =3880)
Age, mean (SD)	55.0 (7.7)	53.7 (6.8)	53.2 (7.4)	52.0 (7.4)	54.2 (7.5)
Sex n (%)					
Male	750 (32.2)	66 (25.4)	656 (58.9)	84 (46.9)	1556(40.1)
Female	1577 (67.8)	194 (74.6)	458 (41.1)	95 (53.1)	2324 (59.9)
Household income n (%)					
Lower income level (<49,999 \$)	631 (27.1)	110 (42.3)	298 (26.8)	67 (37.4)	1106 (28.5)
Middle income level (50,000 – 149,999 \$)	1429 (61.4)	132 (50.8)	694 (62.3)	103 (57.5)	2358 (60.8)
High income level (>150,000 \$)	267 (11.5)	18 (6.9)	122 (11.0)	9 (5.0)	416 (10.7)
Postsecondary education n (%)					
No	441 (19.0)	72 (27.7)	275 (24.7)	58 (32.4)	846 (21.8)
Yes	1886 (81.0)	188 (72.3)	839 (75.3)	121 (67.6)	3034 (78.2)
Born in Canada n (%)					
No	241 (10.4)	39 (15.0)	94 (8.4)	23 (12.8)	397 (10.2)
Yes	2086 (89.6)	221 (85.0)	1020 (91.6)	156 (87.2)	3483 (89.8)

Ethnicity n (%)					
Other	170 (7.3)	25 (9.6)	63 (5.7)	13 (7.3)	271 (7.0)
White	2157 (92.7)	235 (90.4)	1051 (94.3)	166 (92.7)	3609 (93.0)
Marital status n (%)					
Married/partner	1583 (68.0)	131 (50.4)	778 (69.8)	103 (57.5)	2595 (66.9)
Single	277 (11.9)	53 (20.4)	158 (14.2)	39 (21.8)	527 (13.6)
Divorced/separated/widowed	467 (20.1)	76 (29.2)	178 (16.0)	37 (20.7)	758 (19.7)
Daily alcohol consumption n (%)					
No	2020 (86.8)	234 (90.0)	993 (89.1)	168 (93.9)	3415 (88.0)
Yes	307 (13.2)	26 (10.0)	121 (10.9)	11 (6.1)	465 (12.0)
Smoking status n (%)					
Daily and occasional	283 (12.2)	53 (20.4)	203 (18.2)	42 (23.5)	581 (15.0)
Past smoking	988 (42.4)	102 (39.2)	447 (40.1)	60 (33.5)	1597 (41.2)
Never smoking	1056 (45.4)	105 (30.4)	464 (41.7)	77 (43.0)	1702 (43.9)
Physical activity n (%)					
No	1405 (60.4)	182 (70.0)	646 (58.0)	126 (70.4)	2359 (60.8)
Yes	922 (39.6)	78 (30.0)	468 (42.0)	53 (29.6)	1521 (39.2)

Diabetes incidence n (%)					
No	2189 (94.1)	242 (93.1)	1023 (91.8)	163 (91.1)	3617 (93.2)
Yes	138 (5.9)	18 (6.9)	91 (8.2)	16 (8.9)	263 (6.8)
UPF consumption grams/day, mean (SD)	102.9 (43.7)	106.1 (46.2)	449.4 (436.1)	605.4 (711.5)	225.8 (331.8)

LUND, lower/middle tertile of ultra-processed foods consumption and low depressive symptoms; LUD, lower/middle tertile of ultra-processed foods consumption and high depressive symptoms; HUND, higher tertile of ultra-processed foods consumption and low depressive symptoms; HUD, higher tertile of ultra-processed foods consumption and high depressive symptoms; UPF, Ultra-processed foods.

Table 3.3 Results of Cox regression for UPF consumption and depression assessed using PHQ-9 and anti-depressant for incident type 2 diabetes

Groups	N	Incident T2D	Unadjusted Model, HR (95% CI)	Age- and Sex-Adjusted Model, HR (95% CI)	Fully Adjusted Model, HR (95% CI) *
Model 1: UPF consumption univariate association					
Lower tertile of UPF consumption	1293	70	Reference	Reference	Reference
Middle tertile of UPF consumption	1294	86	1.23 (0.90 - 1.69)	1.20 (0.87 - 1.66)	1.26 (0.91 - 1.74)
Higher tertile of UPF consumption	1293	107	1.55 (1.15 - 2.10)	1.50 (1.09 - 2.07)	1.47 (1.07 - 2.03)
Model 2: Depression univariate association					
PHQ-9 summary score (< 6) Low	3441	229	Reference	Reference	Reference
PHQ-9 summary score (>= 6) High	439	34	1.18 (0.82 - 1.69)	1.34 (0.93 - 1.93)	1.22 (0.85 - 1.76)
Model 3: Anti-depressant use univariate association					
Anti-depressant use NO	3599	240	Reference	Reference	Reference
Anti-depressant use YES	281	23	1.25 (0.81 - 1.91)	1.39 (0.90 - 2.14)	1.31(0.85 - 2.01)

UPF, Ultra-processed foods; PHQ-9, Patient Health Questionnaire-9.

*Fully adjusted model is adjusted for the following variables: age, sex, household income, education, ethnicity, born in Canada, smoking status, physical activity, daily alcohol consumption.

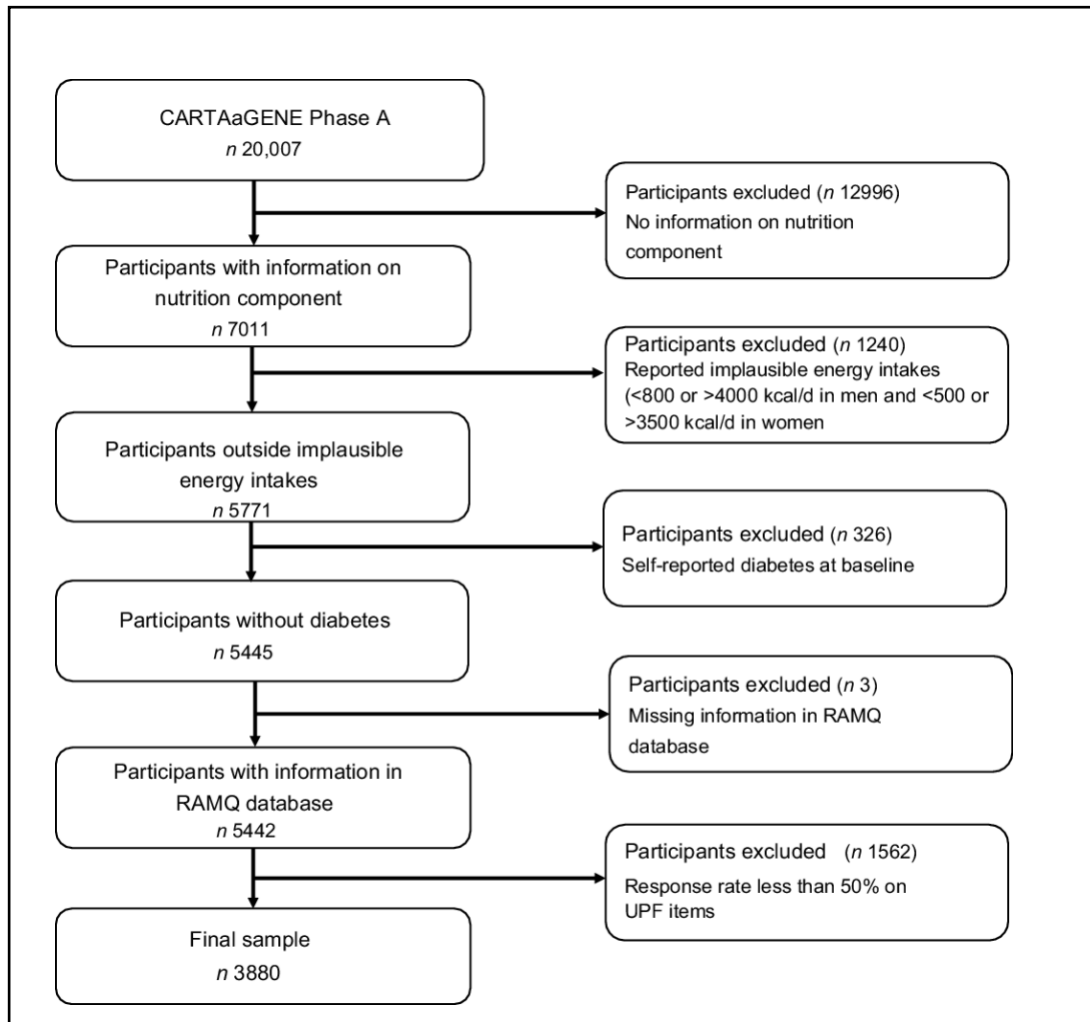
Table 3.4 Results of Cox regression for UPF consumption and depression assessed using PHQ-9 and anti-depressant joint association for incident type 2 diabetes

Groups	N	Incident T2D (N)	Unadjusted Model, HR (95% CI)	Age- and Sex- Adjusted Model, HR (95% CI)	Fully Adjusted Model, HR (95% CI) *
Model 1 UPF consumption lower & middle tertile combined and depressive symptoms joint association					
LUND	2327	138	Reference	Reference	Reference
LUD	260	18	1.17 (0.72 - 1.92)	1.32 (0.80 - 2.15)	1.21 (0.73 - 1.98)
HUND	1114	91	1.39 (1.07 - 1.81)	1.34 (1.02 - 1.77)	1.28 (0.97 - 1.69)
HUD	179	16	1.56 (0.93 - 2.62)	1.75 (1.04 - 2.95)	1.58 (0.93 - 2.68)
Model 2 UPF consumption lower & middle tertile combined and depressive symptoms/Antidepressant use joint association					
LUNDA	2207	127	Reference	Reference	Reference
LUDA	380	29	1.34 (0.89 - 2.01)	1.49 (0.99 - 2.23)	1.38 (0.92 - 2.07)
HUNDA	1046	85	1.43 (1.08 - 1.88)	1.37 (1.03 - 1.82)	1.31 (0.98 - 1.74)
HUDA	247	22	1.60 (1.02 - 2.51)	1.78 (1.13 - 2.81)	1.62 (1.02 - 2.57)

LUND, lower/middle tertile of ultra-processed foods consumption and low depressive symptoms; LUD, lower/middle tertile of ultra-processed foods consumption and high depressive symptoms; HUND, higher tertile of ultra-processed foods consumption and low depressive symptoms; HUD, higher tertile of ultra-processed foods consumption and high depressive symptoms; LUNDA, lower and middle tertile of ultra-processed foods consumption and low depressive symptoms and no antidepressant use; LUDA, lower and middle tertile of ultra-processed foods consumption and high depressive symptoms or antidepressant use; HUNDA, higher tertile of ultra-processed foods consumption and low depressive symptoms and no antidepressant; HUDA, higher tertile of ultra-processed foods consumption and high depressive symptoms or antidepressant.

*Fully adjusted model is adjusted for the following variables: age, sex, household income, education, ethnicity, born in Canada, smoking status, physical activity, daily alcohol consumption.

Figure 3.1 Flow diagram of the final sample for the analysis



RAMQ, Régie de l'Assurance Maladie du Québec; UPF, Ultra-processed foods

Supplementary material for Chapter 3

We performed two sensitivity analyses, by performing the Cox regressions first with a 40% and second with a 60% response rate on the ultra-processed food and beverage items.

1. 40% response rate 15 questions out of 37 on UPF, sample size n = 4365

Supplementary Table 3.1 Results of cox regression for UPF consumption and depression assessed using PHQ-9 and anti-depressant for incident type 2 diabetes in CARTaGENE (40% response rate)

Groups	N	Unadjusted Model, HR (95% CI)	Age- and Sex-Adjusted Model, HR (95% CI)	Fully Adjusted Model, HR (95% CI) *
Model 1: UPF consumption univariate association				
Lower tertile of UPF consumption	1454	Reference	Reference	Reference
Middle tertile of UPF consumption	1455	1.32 (0.99 - 1.77)	1.29 (0.96 - 1.73)	1.34 (1.00 - 1.81)
Higher tertile of UPF consumption	1455	1.47 (1.1 - 1.96)	1.43 (1.06 - 1.94)	1.40 (1.03 - 1.89)
Model 2: Depression univariate association				
PHQ-9 summary score (< 6) Low	3861	Reference	Reference	Reference
PHQ-9 summary score (>= 6) High	503	1.14 (0.81 - 1.60)	1.28 (0.91 - 1.80)	1.15 (0.91 - 1.63)
Model 3: Anti-depressant use univariate association				
Anti-depressant use NO	4043	Reference	Reference	Reference
Anti-depressant use YES	321	1.22 (0.82 - 1.83)	1.36 (0.94 - 2.08)	1.30 (0.86 - 1.95)

UPF, Ultra-processed foods; PHQ-9, Patient Health Questionnaire-9.

*Fully adjusted model is adjusted for the following variables: age, sex, household income, education, ethnicity, born in Canada, smoking status, physical activity, daily alcohol consumption.

Supplementary Table 3.2 Results of cox regression for UPF consumption and depression assessed using PHQ-9 and anti-depressant joint association for incident type 2 diabetes in CARTaGENE (40% response rate)

Groups	N	Unadjusted Model, HR (95% CI)	Age- and Sex-Adjusted Model, HR (95% CI)	Fully Adjusted Model, HR (95% CI) *
Model 1 UPF consumption lower & middle tertile combined and depressive symptoms joint association				
LUND	2323	Reference	Reference	Reference
LUD	264	1.00 (0.60 - 1.68)	1.12 (0.66 - 1.88)	1.00 (0.59 - 1.69)
HUND	1118	1.31 (1.00 - 1.71)	1.26 (0.95 - 1.65)	1.21 (0.92 - 1.59)
HUD	175	1.76 (1.07 - 2.87)	1.98(1.20 - 3.24)	1.80 (1.01 - 2.98)
Model 2 UPF consumption lower & middle tertile combined and depressive symptoms/Antidepressant use joint association				
LUNDA	2205	Reference	Reference	Reference
LUDA	382	1.21 (0.82 - 1.84)	1.35 (0.89 - 2.04)	1.24 (0.82 - 1.89)
HUNDA	1048	1.34 (1.02 - 1.77)	1.28 (0.96 - 1.70)	1.23 (0.93 - 1.66)
HUDA	245	1.72 (1.11 - 2.65)	1.92 (1.24 - 3.00)	1.76 (1.13 - 2.74)

LUND, lower/middle tertile of ultra-processed foods consumption and low depressive symptoms; LUD, lower/middle tertile of ultra-processed foods consumption and high depressive symptoms; HUND, higher tertile of ultra-processed foods consumption and low depressive symptoms; HUD, higher tertile of ultra-processed foods consumption and high depressive symptoms; LUNDA, lower and middle tertile of ultra-processed foods consumption and low depressive symptoms and no antidepressant use; LUDA, lower and middle tertile of ultra-processed foods consumption and high depressive symptoms or antidepressant use; HUNDA, higher tertile of ultra-processed foods consumption and low depressive symptoms and no antidepressant; HUDA, higher tertile of ultra-processed foods consumption and high depressive symptoms or antidepressant.

*Fully adjusted model is adjusted for the following variables: age, sex, household income, education, ethnicity, born in Canada, smoking status, physical activity, daily alcohol consumption.

2. 60% response rate 22 questions out of 37 on UPF, sample size n = 3012

Supplementary Table 3.3 Results of cox regression for UPF consumption and depression assessed using PHQ-9 and anti-depressant for incident type 2 diabetes in CARTaGENE (60% response rate)

Groups	N	Unadjusted Model, HR (95% CI)	Age- and Sex-Adjusted Model, HR (95% CI)	Fully Adjusted Model, HR (95% CI) *
Model 1: UPF consumption univariate association				
Lower tertile of UPF consumption	1004	Reference	Reference	Reference
Middle tertile of UPF consumption	1004	1.25 (0.88 - 1.76)	1.26 (0.89 - 1.79)	1.37 (0.96 - 1.95)
Higher tertile of UPF consumption	1004	1.45 (1.03 - 2.02)	1.50 (1.06 - 2.12)	1.52 (1.07 - 2.17)
Model 2: Depression univariate association				
PHQ-9 summary score (< 6) Low	2655	Reference	Reference	Reference
PHQ-9 summary score (>= 6) High	357	1.19 (0.80 - 1.76)	1.32 (0.89 - 1.96)	1.21 (0.81 - 1.81)
Model 3: Anti-depressant use univariate association				
Anti-depressant use NO	2796	Reference	Reference	Reference
Anti-depressant use YES	216	1.37 (0.87 - 2.18)	1.46 (0.92 - 2.31)	1.41 (0.88 - 2.24)

UPF, Ultra-processed foods; PHQ-9, Patient Health Questionnaire-9.

*Fully adjusted model is adjusted for the following variables: age, sex, household income, education, ethnicity, born in Canada, smoking status, physical activity, daily alcohol consumption.

Supplementary Table 3.4 Results of cox regression for UPF consumption and depression assessed using PHQ-9 and anti-depressant joint association for incident type 2 diabetes in CARTaGENE (60% response rate)

Groups	N	Unadjusted Model, HR (95% CI)	Age- and Sex-Adjusted Model, HR (95% CI)	Fully Adjusted Model, HR (95% CI) *
Model 1 UPF consumption lower & middle tertile combined and depressive symptoms joint association				
LUND	1789	Reference	Reference	Reference
LUD	219	1.07 (0.63 - 1.84)	1.19 (0.69 - 2.04)	1.08 (0.63 - 1.87)
HUND	866	1.25 (0.93 - 1.68)	1.27 (0.93 - 1.73)	1.24 (0.91 - 1.67)
HUD	138	1.62 (0.93 - 2.83)	1.84 (1.05 - 3.217)	1.67 (0.96 - 2.97)
Model 2 UPF consumption lower & middle tertile combined and depressive symptoms/Antidepressant use joint association				
LUNDA	1700	Reference	Reference	Reference
LUDA	308	1.27 (0.81 - 1.98)	1.39 (0.89 - 2.16)	1.30 (0.83 - 2.04)
HUNDA	812	1.27 (0.93 - 1.74)	1.29 (0.94 - 1.78)	1.26 (0.91 - 1.74)
HUDA	192	1.63 (1.00 - 2.66)	1.82 (1.11 - 2.97)	1.69 (1.03 - 2.78)

LUND, lower/middle tertile of ultra-processed foods consumption and low depressive symptoms; LUD, lower/middle tertile of ultra-processed foods consumption and high depressive symptoms; HUND, higher tertile of ultra-processed foods consumption and low depressive symptoms; HUD, higher tertile of ultra-processed foods consumption and high depressive symptoms; LUNDA, lower and middle tertile of ultra-processed foods consumption and low depressive symptoms and no antidepressant use; LUDA, lower and middle tertile of ultra-processed foods consumption and high depressive symptoms or antidepressant use; HUNDA, higher tertile of ultra-processed foods consumption and low depressive symptoms and no antidepressant; HUDA, higher tertile of ultra-processed foods consumption and high depressive symptoms or antidepressant.

*Fully adjusted model is adjusted for the following variables: age, sex, household income, education, ethnicity, born in Canada, smoking status, physical activity, daily alcohol consumption.

Bridge Statement 1

The results of the first manuscript confirmed that participants with both elevated depression and high UPF consumption at baseline might be at an increased risk of developing T2D compared to those with high depression only and those with high UPF consumption only or neither. Further, depression among T2D was often associated with poor adherence to lifestyle, such as not eating a healthy diet. Individuals with comorbid depression and high UPF consumption might be at a particularly increased risk of diabetes complications. It is possible that depression and high UPF consumption may exacerbate physiological processes, such as systemic inflammation, which is a risk factor for T2D complications. To my knowledge, no previous studies have examined the combined effect of depression and UPF consumption on diabetes complications. To address that gap, the second manuscript investigated the combined effect of depression and UPF consumption on diabetes complications in a community-based sample of adults with type 2 diabetes.

Chapter 4: Manuscript 2. Ultra-processed foods consumption, depression, and the risk of diabetes complications in the CARTaGENE project: A prospective cohort study in Quebec, Canada

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Abstract

Introduction: This study aimed to assess the association between depression, ultra-processed food consumption (UPF), and the risk of developing diabetes-specific complications in adults with type 2 diabetes (T2D).

Methods: Baseline data came from the CARTaGENE study, a health survey of adults (40–69 years) in Quebec, Canada. The incidence of T2D complications was examined in N= 683 participants with T2D without complications at baseline by linking survey data with administrative health data. Food and drink consumption was assessed using the Canadian Diet History Questionnaire and categorized by NOVA classification. Participants were categorized into tertiles of UPF consumption. Depression was defined as having elevated depressive symptoms based on the Patient Health Questionnaire-9 or the use of antidepressant medications. Cox regression models were used to estimate the associations between UPF, depression, and T2D complications.

Results: In total, 105 individuals developed diabetes-related complications over a 7-year period. Participants with high depressive symptoms and high UPF consumption had the highest risk for diabetes complications (adjusted hazard ratio (aHR) 2.07, 95% CI: 0.91 – 4.70), compared to participants with low depressive symptoms and low UPF consumption. Higher risks for diabetes complications were observed when high depressive symptoms and antidepressant use were combined with high UPF consumption (aHR 2.59, 95% CI: 1.32 – 5.06).

Conclusions: This study indicates that those with co-occurring depression and high UPF consumption have a greater risk of diabetes complications. Early management and monitoring of both risk factors might be essential to prevent diabetes complications.

Keywords: Ultra-processed food¹, Depressive symptoms², Type 2 diabetes complication³, Interaction⁴, CARTaGENE⁵.

Introduction

Type 2 diabetes (T2D) is a chronic metabolic condition which requires intensive self-care management (1). Adopting and/or maintaining a healthy diet remains one of the main strategies for the management of T2D and its complications (2). Research has demonstrated that following healthy diets such as the Mediterranean diet (high in olive oil, fruit, nuts, vegetables, and cereals intakes) can reduce the risk of micro-and macrovascular complications among individuals with T2D (3-6).

Recently, in many modern food systems, there has been a nutritional transition characterized by an increase in the consumption of ultra-processed foods (UPF) as a replacement for fresh foods (7). UPF are defined as “multi-ingredient industrial formulations” which are characterized by low nutritional quality, high energy density, high saturated and trans fats content, added sugars and salt, and low protein, dietary fiber, and micronutrients (7, 8). Further, UPF are often designed in a way to encourage eating them in combination (e.g., savory snacks with soft drinks), which can result in excessive caloric intake (7, 8). It has been reported that in higher-income countries, such as the United States and Canada, UPF can contribute to half of the daily dietary energy intake (9, 10). Higher consumption of UPF can increase the risk of numerous chronic conditions such as T2D, metabolic syndrome, depression, all-cause mortality, and cardiovascular diseases (9).

Among individuals with T2D, UPF consumption may increase the risk of developing complications related to T2D. For instance, a recent study found that in individuals with T2D, high consumption of processed foods was associated with poor glycemic control and a greater likelihood of microvascular complications (11). UPF are associated with elevated levels of glucose (12), which can result in the development of advanced glycation end-products (AGEs).

AGEs can activate inflammatory signaling cascades and, consequently, have a crucial role in the pathogenesis of diabetes complications (13).

T2D is a multifactorial disease with psychological complications in addition to physical complications. The risk of developing depressive symptoms is more common in individuals with T2D than in the general population (14). Comorbid depression among individuals with T2D is associated with adverse health outcomes such as micro-and macrovascular complications and higher mortality rates (15). A meta-analysis of longitudinal studies showed that depression was linked with an increased risk of microvascular (HR=1.33; 95% CI: 1.25–1.41) and macrovascular complications (HR=1.38; 95% CI: 1.30–1.47) among adults with T2D (15).

Further, persons with comorbid depression and T2D might have more difficulties following a healthy diet, thereby potentially further increasing the risk of complications (11). Prior research has demonstrated that a history of depression and higher severity of depression was associated with higher emotional and uncontrolled eating, often leading to higher calorie consumption (16). A previous study has also reported an association between depression and high UPF consumption (17).

Consumption of unhealthy foods such as UPF and high depressive symptoms can independently increase the risk of diabetes-related complications among individuals with T2D (9, 15). It is currently unknown whether high depressive symptoms among individuals with T2D compounds the potential impact of UPF consumption on the risk of diabetes-related complications. It is possible that depressive symptoms and UPF consumption may exacerbate the physiological processes, such as systemic inflammation which is risk factor for the T2D and its complications (18, 19, 20). Moreover, in a previous study, we found an important interaction between depressive symptoms and UPF consumption on the risk of developing T2D (21). Adults

with both depressive symptoms and high UPF consumption had a higher risk of developing T2D within a seven-year interval than those without depressive symptoms and with low UPF consumption (21).

As a next step, we aim to investigate a potential additive interaction between UPF consumption and depressive symptoms on the incidence of diabetes-related complications in adults with T2D. The combination of depression and consumption of UPF might not only increase the risk of developing T2D but might also increase the risk of developing diabetes-specific complications in adults with T2D. We, therefore, hypothesized that individuals with T2D with both depressive symptoms and high UPF consumption at baseline would have a higher risk of developing micro-and macrovascular complications, compared to those without depressive symptoms and with low UPF consumption.

Methods

Study population

The sample was drawn from the baseline CARTaGENE (CaG) (2009–2010) study (22). CaG is a community health survey that gathered detailed information on health, lifestyle, and sociodemographic information, physiological measures, and biological samples from urban areas of Quebec, Canada (22). Participants aged 40–69 years at baseline were randomly recruited from the Régie de l'assurance maladie du Québec (RAMQ), a governmental health insurance database in the Canadian province of Quebec that provides universal health insurance for residents. Details of the study, such as recruitment, enrollment, and data collection methods, are described elsewhere (22). Briefly, the CaG survey design defined by two age groups, gender, and forward sortation area (defined by 3-digit postal codes). Probability proportional to size was used to describe quotas for each stratum. Participants were excluded if they were not registered in the

RAMQ database, those residing outside selected regions, individuals in First Nations Reserves or long-term health care facilities or were in prison (22). Various strategies were employed to ensure response rates and minimize attrition, such as (i) utilizing the reputable governmental body RAMQ to handle participant contact and identifying information, (ii) implementing systematic methods for contact, scheduling, and reminders, and (iii) offering a financial compensation of \$45 (22). The recruitment process involved a call center at RAMQ to prevent the transfer of identifying information to CaG. Information packages were initially mailed, followed by telephone contact to enroll participants and schedule clinical assessment site interviews. A total of 20, 007 participants provided informed consent to participate in the CaG cohort study and agreed to link their data with the RAMQ database (22). Ethical approval was provided by the Douglas Mental Health University Institute Research Ethics Board and the St. Justine Hospital Research Ethics Board. Follow-up data referring to T2D complication incidence were obtained by linking participants with diagnostic codes from the RAMQ database.

Measures

Depressive symptoms

Depressive symptoms experienced within the past two weeks were measured using the Patient Health Questionnaire-9 (PHQ-9) (23). The PHQ-9 consists of nine questions related to vegetative, emotional, behavioral, and cognitive symptoms of depression. Responses are rated on a 4-point scale ranging from 0 “not at all” to 3 “every day”, with a summary score ranging from 0 to 27, with higher scores reflecting greater depressive symptom severity. The PHQ-9 has shown good agreement with a clinical diagnosis of major depressive disorder and good validity and reliability (23). In the present study, elevated depressive symptoms were defined as having a PHQ-9 summary score of 6 and higher, which includes mild to severe depressive symptoms.

This cut-off score has been used in previous studies included in the CaG cohort (24, 25). When compared with the fully structured interviews for major depressive disorder, a PHQ-9 cut-off of 6 has a sensitivity of 0.91 and specificity of 0.61 (26).

Antidepressant use

Participants brought their current medication or reported their current medication at the baseline CaG interview. Medication was classified as an antidepressant based on the medication name (27).

Dietary intake assessment

Dietary intake in the CaG survey was assessed at baseline using the Canadian-adapted diet history questionnaire II (C-DHQ II) (22). C-DHQ II is a validated food frequency questionnaire (FFQ) which reflects food availability, brand names, nutrition composition, and food fortification in Canada (28, 29).

Frequency of consumption and portion sizes are defined for most of the food items in FFQ. Daily consumption of each FFQ food item was computed based on one of four units of time, depending on which answer choice was selected: year, month, week, or day (30). To calculate the daily consumption of each FFQ item, consumption frequency of the items was first converted into daily equivalents such never = 0; 1-6 times per year = 0.01; 7-11 times per year = 0.02; 1 time per month = 0.03; 2-3 times per month = 0.07; 1 time per week = 0.14; 2 times per week = 0.29; 3-4 times per week = 0.48; 5-6 times per week = 0.74; 1 time per day = 1; 2 or more times per day = 3, as specified by the C-DHQII database (31). Secondly, portions of consumed food items were converted into grams by using the nutrient database for the C-DHQII (31). Portions are sex-specific and based on the percentiles of intake reported in the Canadian Community Health Survey (CCHS) – Cycle 2.2 Nutrition (28, 29). The consumed amount for

every food item was then calculated by multiplying the frequency per day and grams of consumption. In the present analysis, food items without portion size and items such as vitamins, minerals, or herbal supplements were excluded. Further, items of the C-DHQ II with missing information were filled in with zero imputation, based on the assumption that non-response to the items may be because those items were not consumed by the participants (32).

Every C-DHQ II reported food and beverage item was categorized into one of the four NOVA classification groups. NOVA is not an acronym, but a classification system that groups foods according to the nature, extent, and purpose of the industrial processing (7). Foods were classified into four different groups: 1) unprocessed or minimally processed foods which includes fruit and vegetables, grains (cereals), fresh or pasteurized milk products, seeds without oil and salt, legumes, meat, and fish; 2) processed culinary ingredients such as salt, sugar, vegetable oil, and butter; 3) processed foods, such as canned vegetables and fruits, cheeses, and freshly made bread; and 4) ultra-processed foods and drinks (UPF) that were prepared mostly or entirely from substances derived from foods, derived from food constituents, or produced in the laboratories from food substrates or other organic sources. Examples of products are ready-to-eat meals, carbonated drinks, biscuits, processed meat, and sugared milk and fruit drinks (7).

To estimate the frequency of consumption of UPF (grams/day), we summed the amount consumed (grams/day) of each food and beverage item classified in the fourth category of the NOVA classification (a total of 30 foods and seven beverage items). Next, we divided the sample into tertiles according to the total consumption of UPF (grams/day). Low and middle tertiles were merged as one group for analysis (21).

Incidence of T2D complications

The study outcomes included micro-and macrovascular diabetes complications. Complications were assessed using diagnostic codes in the RAMQ billing database. Diagnostic codes were based on the World Health Organization's International Classification of Diseases, 9th or 10th edition (ICD-9 and ICD-10, respectively). Codes for micro-and macrovascular diabetes complications in ICD-9 and ICD-10 were based on prior literature and can be found in Supplementary Table 1. For the main analysis, micro-and macrovascular complications were combined. Participants were followed for up to seven years using administrative data from the date of their CaG baseline assessment. The date of the first diagnosis for micro-and macrovascular diabetes complications was recorded. Observational time was calculated from the day of baseline assessment to the day of complication onset, the date of death, or the study end date of December 31, 2016.

Confounders

Potential confounders include sociodemographic characteristics (age, sex, annual household income, education, and self-reported ethnicity (white was compared with others groups for analysis), behavioral factors including alcohol consumption, defined as whether participants consume alcohol daily or not, smoking ("currently smokes daily or occasionally", "past smoker", or has "never smoked"), physical activity (five or more-day moderate activity in a week or three or more vigorous in a week), and body mass index (BMI, continuous) (15).

Statistical analysis

Inclusion criteria

Only CaG participants with information on the nutrition component, depressive symptoms and diabetes status at baseline were included (n = 7,011) (21). Furthermore, the sample was restricted to participants with diabetes and without diabetes complications at baseline

(n = 881). Diabetes was self-reported based on a diagnosis made by a physician on a positive response to the following question: ‘Has a doctor ever told you that you had diabetes?’ or HbA1c levels equal to or above 6.5 during the CAG baseline assessment. We excluded all participants who reported implausible energy intakes <800 or >4000 kcal/d in men and <500 or >3500 kcal/d in women (n = 52) as reported in previous research (33). Implausible reporting, particularly underreporting, is a commonly recognized limitation of dietary assessment methods; participants tend to underestimate their total energy intakes and underreport intakes of foods that are deemed unhealthy or socially undesirable, such as foods that are high in fat and refined carbohydrates (33). Further, we excluded participants whose response rates were less than 50% on the UPF items (n = 146). A total of N = 683 participants were included for the analyses (**figure 4.1**). Moreover, we performed two sensitivity analyses, first with a 40% response rate on UPF items (sample size n = 814) and second with a 60% response rate on the UPF items (sample size n = 561) to test the robustness of the study.

Cox proportional hazards models were conducted to examine the univariate associations between UPF consumption, depressive symptoms, and antidepressant use with diabetes complications incidence. Micro-and macrovascular complications were combined for the analysis due to small sample size. However, they were also examined separately in secondary analysis.

To evaluate the potential additive interaction on the incidence of diabetes complications, four groups were defined based on the presence/absence of depressive symptoms and low/high intake of UPF. The groups were: 1) lower/middle tertile of UPF consumption and low depressive symptoms (LUND as the reference group), 2) lower/middle tertile of UPF consumption and elevated depressive symptoms (LUD), 3) higher tertile of UPF consumption and low depressive

symptoms (HUND), and 4) higher tertile of UPF consumption and elevated depressive symptoms (HUD).

Further, an additional analysis was performed combining depressive symptoms with antidepressant medications as an indicator for depression. Similarly to our primary analyses, four groups were created: 1) lower/middle tertile of UPF consumption and low depressive symptoms and no antidepressant use (LUNDA as the reference group), 2) lower/middle tertile of UPF consumption and elevated depressive symptoms or antidepressant use (LUDA), 3) higher tertile of UPF consumption and low depressive symptoms and no antidepressant use (HUNDA), and 4) higher tertile of UPF consumption and elevated depressive symptoms or antidepressant use (HUDA). All Cox regression analyses were performed in unadjusted models, in models adjusted for age and sex only, and in fully adjusted models for all the confounders described above. Hazard ratios [HRs] with 95% confidence intervals are reported. Missing information on the covariates was imputed using the fully conditional specification with discriminant or logistic methods using PROC MI procedure in SAS. Cox regression analyses were conducted using SPSS software.

Results

The main food group contributors to UPF intake are shown in Table 4.1. Overall, mean (SD) consumption of the UPF was 276.9 (SD 421.0) g/d, and mean consumption in lower, middle, and highest tertiles was 71.5 (2 SD 3.6) g/d, 154.2 (SD 29.8) g/d, and 604.0 (SD 605.3) g/d, respectively.

Table 4.22 displays the characteristics of the sample. The baseline data reveals a mean age of 55.5 years (SD = 7.5), with 52.6% being female and 93.3% identifying as white. A total of 105 (15.4%) individuals developed diabetes-related complications during the observation period.

Using the categorical classifications for groups based on UPFs and PHQ-9 scores, there were 395 (57.0 %) participants in LUND group (reference group); 60 (8.9 %) participants in LUD group; 191 (28.8 %) participants in HUND group; and 37 (5.3 %) participants in HUD group. Participants in the HUD group exhibited a higher percentage of lower-income levels and a lower percentage of postsecondary education compared to the other group. Additionally, individuals in the HUD group were more likely to be daily or occasional smokers and physically inactive compared to the other group. Moreover, the HUD group had a higher mean intake of UPFs 615.2 (478.2) g/d, and a higher BMI 31.0 (6.2) as compared to the other groups.

Table 4.3 describes the results of three univariate Cox regression analyses examining UPF, depressive symptoms, and antidepressant use. Participants in the highest tertile of UPF consumption had the greatest hazard ratios for developing complications in the fully adjusted model (HR=1.56, 95% CI: 0.92-2.62); however, the CI were overlapping with the one. Similarly, the CI overlapped with one in a fully adjusted model for depressive symptoms (PHQ-9 $\geq$ 6) and for antidepressant use with HRs of 1.45 (95% CI: 0.84- 2.51) and 1.61 (95% CI: 0.86 – 3.00) respectively.

Table 4.4 shows results obtained from the additive interaction analysis, with the reference category in model 1 set as the LUND group. In HUD group, 24.3% of individuals developed complications. In the age and sex-adjusted model, the HUD group had a 2.4-fold increased risk of developing complications as compared to the LUD and HUND group. However, in the fully adjusted model, HUD group HR was 2.07 (95% CI: 0.91 – 5.06), and CI overlapped with one.

Further in model 2, when elevated depressive symptoms and antidepressant medication were combined as indicators for depression, 28.6% of individuals developed T2D complications. And similarly greater risk for T2D complications was found in the HUD group in the model

adjusted for age and sex (2.82, 95% CI: 1.53-5.18). Moreover, in a fully adjusted model, the HR was 2.59 (95% CI: 1.32-5.06).

We also performed separate analyses for microvascular complications. The results are not presented in the tables because of the small sample size. For micro complications, there were 37 individuals in group HUD, and out of these individuals, only 8 individuals developed the micro complication with an adjusted HR of 2.64 (95% CI: 1.06 – 6.54) (Supplementary Table 4.2). Moreover, two sensitivity analysis showed similar results, suggesting that participants in the depressive symptoms and UPF consumption groups had higher hazard ratios for developing diabetes complications than those with either condition alone (Supplementary Table 4.3 & 4.4).

Discussion

In this prospective study, we examined the associations between UPF consumption, depressive symptoms, and the risk of developing T2D complications among middle-aged adults by linking survey data with administrative data. We found that individuals with depressive symptoms and higher consumption of UPF at baseline had a higher risk of developing T2D related micro-and macro complications in a model adjusted for sex and age as compared to those with neither condition, and this risk estimate was higher than those with depressive symptoms only and those with high UPF consumption only. Further, when depressive symptoms and higher consumption of the UPF group were controlled for additional confounders in the fully adjusted model, the HRs were lowered and included 1.00 in the CI. However, when depressive symptoms and antidepressant medication use were combined as indicators for depression, then the combination of both resulted in the CI that did not include 1.00 in the fully adjusted model. These results suggest an interaction between depression and UPF consumption in relation to an increased risk of diabetes-related complications.

To our knowledge no study in the past directly investigated this interaction. One study has reported that T2D individuals with food addiction, which is associated with UPF consumption (34), had a greater prevalence of diabetes retinopathy, neuropathy, nephropathy, and depressive symptoms compared to those without food addictions (11).

There are several pathways in which depression or depressive symptoms may be associated with an increased risk of developing diabetes complications. One of the potential pathways by which depression among T2D individuals might increase the risk of diabetes-related complications is through suboptimal diabetes management (14, 15). It has been reported that individuals with T2D and high depressive symptoms tend to have lower adherence to medication, diet, and exercise than individuals with T2D alone (15). In addition, depression can be accompanied by behavioural changes, such as reduced self-care and medication adherence, increased intake of high-calorie food, smoking, reduced physical activity, and increased sedentary behaviors (15). These behaviors might have more detrimental effects in the context of diabetes, possibly resulting in poor glycemic control, which, in turn, may be associated with an increased risk of complications (15).

Diabetes with comorbid depressive symptoms is associated with increased hypothalamic–pituitary–adrenal axis and sympathetic nervous system activation (14). Further, increased insulin resistance and high concentration of inflammatory markers may lead to complications in individuals with comorbid diabetes and depression (14, 18). Depressive symptoms and UPF are also independently associated with inflammatory markers such as C-reactive protein, tumour necrosis factor- α , interleukin-1, and interleukin-6 levels (18, 19). UPF often occur within high obesogenic environments and have higher glycemic loads (18, 19). These diets may induce hyperglycemia, which is associated with increased pro-inflammatory cytokines, including IL-6

and TNF- α , leading to insulin resistance by disruptions in insulin signalling and subsequently might increase the risk of the diabetes complications (13). Besides the nutritional aspects of UPF, recent concern has emerged on changes in microbiota induced by non-nutritive components, mainly by flavors, emulsifiers, and thickeners, which may provoke gut dysbiosis and initiate inflammation in the gut (35). However, more research is needed to better understand the relative effects of UPF on diabetes related complication incidence.

Furthermore, antidepressants use is one of the standard treatments for depressive disorders (36). However, certain antidepressants can increase the risk of body weight and poor glycemic control (36), which might lead to diabetes-related complications (37). Our study shows that; when antidepressant use and depressive symptoms were combined with high UPF consumption, the risk of diabetes complications was higher than the depressive symptoms combined with high UPF consumption.

Strengths and limitation

Strengths of this study include its prospective design, the use of two different measures for depression, the combined use of survey data with administrative health data, and adjustment for potential confounders. Further, two sensitivity analyses using two different response rates on UPF consumption were conducted to assess the robustness of the study findings. Acknowledging that the data is 13 years old, we also acknowledge the general challenge of low response rates to food frequency questionnaires in epidemiological studies focusing on nutrition and health outcomes. Despite the age of the data, this study plays a crucial role in addressing a gap in the literature. By examining the combined impact of depression and UPF consumption, two significant modifiable risk factors, it provides valuable insights into how they jointly influence the risk of diabetes related complications.

There are also various limitations that should be noted. First, the C-DHQ II used in this study was designed to evaluate the intake of major food groups, energy, and macronutrients, not specifically to collect data about the NOVA classification of UPF consumption. Further, there is also limitation related to NOVA classification. Because of its complex and multidimensional definition of levels of food processing, there is a potential for introducing ambiguity and variations in interpretation related to UPF (38). Assessment of the diet intake was self-reported and only measured at the baseline; therefore, it might be possible that participants change their intake of ultra-processed foods during the follow-up. Participants of the CaG study were volunteers in a nutrition component, and thus it may be possible that these individuals were more interested in nutritional issues and healthy lifestyles than the general population. And it might be possible that their consumption of UPF may be lower compared to the general population, which may underestimate the risk investigated in our study. Depressive symptoms were assessed at baseline only. The PHQ-9 is a self-report scale that measures symptoms of depression experienced in the past two weeks and does not consider the history and treatment of depression. Given that depressive symptoms were not measured during the follow-up, symptoms may vary and change over time. Further, another important limitation is that our analysis does not eliminate the possibility that part of this association stems from a shared pathophysiological factor — specifically, the impact of UPF consumption on both diabetes progression/complications and the onset of depression (9). Moreover, there is also limitation with administrative data. In Canada administrative hospital data are produced by health professionals who review, abstract, and code information from inpatient charts following hospital discharge. One of issue with the administrative data is the undercoding of diabetes and its related complications by physicians which can lead to an incomplete representation of the true

prevalence (39). The individual group sizes were small, and therefore studies with large sample size are needed to replicate the findings. CaG participants were mostly white participants (93.3%) and metropolitan; as a result, generalization of our findings should be made with caution.

Conclusion

To conclude, our study suggests that individuals with co-occurring depression and high UPF consumption may represent a group at risk of developing T2D complications. Thus, this group possibly be benefit from greater monitoring and preventive care. However, future research is needed to disentangle the mechanisms linking depression and UPF consumption to T2D complications. In addition, further research is required to replicate these findings in large samples with longer follow-up periods.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions: AS, NS, ASB, SD and HMQ contributed to the study conception, designed the study, and interpreted the analyses. AS conducted the analyses and drafted the manuscript. AS, NS, ASB, SD and HMQ contributed to the revision of the manuscript.

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Table 4.1 Contribution of each food group to the total amount of ultra-processed foods consumed in the CARTaGENE study cohort (*n*=683)

Food groups (<i>n</i> = 37)	Contribution to total ultra-processed foods intake (%) *	Daily amount consumed mean g/d (SD)
<i>Beverages (n=7)</i>		
Dairy beverages	4.2	11.6 (38.8)
Soft/Isotonic drinks	51.2	141.8 (384.3)
Fruit drinks	3.1	8.5 (54.4)
<i>Solid Foods (30)</i>		
Processed meat	4.8	13.3 (30.9)
Fast food and ready to eat	10.8	29.9 (32.9)
Breakfast cereals	3.7	10.3 (16.2)
Cookies, biscuits, muffins, and cake	10.4	28.7 (40.0)
Potato chips and salty snacks	3.0	8.2 (9.7)
Confectionery and chocolate	2.0	5.4 (9.5)
Ketchup, salad dressing and similar	3.9	10.7 (13.5)
Ice-cream	1.9	5.3 (9.8)
Jelly and jams products	1.2	3.2 (6.6)
Total	100	276.9 (421.0)

Contribution (%) of each food group/beverage to the total consumption of ultra-processed food was calculated by dividing the amount (g/d) of each food group by the total amount of ultra-processed foods (g/d) multiplied by 100.

Table 4.2 Baseline characteristics of the study sample

	LUND (n = 395)	LUD (n = 60)	HUND (n = 191)	HUD (n = 37)	Total (n = 683)
Age, mean (SD)	56.2 (7.5)	55.2 (7.5)	54.5 (7.5)	53.7 (5.9)	55.5 (7.5)
Sex n (%)					
Male	163 (41.3)	18 (30.0)	122 (63.9)	21 (56.8)	324 (47.4)
Female	232 (58.7)	42 (70.0)	69 (36.1)	16 (43.2)	359 (52.6)
Household income n (%)					
Lower income level (<49,999 \$)	123 (31.1)	23 (38.3)	55 (28.9)	20 (54.1)	221 (32.4)
Middle income level (50,000 – 149,999 \$)	231 (58.5)	33 (55.0)	117 (61.9)	15 (40.5)	396 (58.0)
High income level (>150,000 \$)	41 (10.4)	4 (6.7)	19 (9.9)	2 (5.4)	66 (9.7)
Postsecondary education n (%)					
No	89 (22.5)	19 (31.7)	51 (26.7)	15 (40.5)	174 (25.5)
Yes	306 (77.5)	41 (68.3)	140 (73.3)	22 (59.5)	509 (74.5)
Born in Canada n (%)					
No	43 (10.9)	14 (23.3)	11 (5.8)	2 (5.4)	70 (10.2)
Yes	352 (89.1)	46 (76.7)	180 (94.2)	35 (94.6)	613 (89.8)
Ethnicity n (%)					

Other	25 (6.3)	10 (16.7)	6 (3.1)	5 (10.9)	60 (6.7)
White	370 (93.7)	50 (83.3)	185 (96.9)	32 (86.5)	637 (93.3)
Marital status n (%)					
Married/partner	270 (68.4)	38 (63.3)	128 (67.0)	26 (70.3)	462 (67.6)
Single	53 (13.4)	9 (15.0)	31 (16.2)	7 (18.9)	100 (14.6)
Divorced/separated/widowed	72 (18.5)	13 (21.7)	32 (16.8)	4 (10.8)	121 (17.7)
Daily alcohol consumption n (%)					
No	342 (86.6)	55 (91.7)	179 (93.7)	35 (94.6)	611 (89.5)
Yes	53 (13.4)	5 (8.3)	12 (6.3)	2 (5.4)	72 (10.5)
Smoking status n (%)					
Daily and occasional	45 (11.4)	11 (18.3)	38 (19.9)	8 (21.6)	102 (14.9)
Past smoking	184 (46.6)	19 (31.7)	82 (42.9)	16 (43.2)	301 (44.1)
Never smoking	166 (42.0)	30 (50.0)	71 (37.2)	13 (35.1)	280 (41.0)
Physical activity n (%)					
Yes	152 (38.5)	17 (28.3)	83 (43.5)	9 (24.3)	261 (38.2)
No	243 (61.5)	43 (71.7)	108 (56.5)	28 (75.7)	422 (61.8)
UPF consumption grams/day, mean (SD)	112.0 (49.7)	118.7 (46.8)	601.8 (628.0)	615.2 (478.2)	276.9 (421.0)
BMI, mean (SD)	27.8 (5.4)	29.0 (6.6)	29.8 (5.9)	31.0 (6.2)	28.6 (5.9)

Diabetes complication n (%)	52 (13.2)	10 (16.7)	34 (17.8)	9 (24.3)	105 (15.4)
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Results reported as mean ± SD for continuous data and n (%) for categorical data. LUND, lower/middle tertile of ultra-processed foods consumption and low depressive symptoms; LUD, lower/middle tertile of ultra-processed foods consumption and high depressive symptoms; HUND, higher tertile of ultra-processed foods consumption and low depressive symptoms; HUD, higher tertile of ultra-processed foods consumption and high depressive symptoms; UPF, Ultra-processed foods

Table 4.3 Results of Cox regression for UPF consumption and depression assessed using PHQ-9 and antidepressant for incident T2D complications

Groups	N	Unadjusted Model, HR (95% CI)	Age- and Sex-Adjusted Model, HR (95% CI)	Fully Adjusted Model, HR (95% CI) *
Model 1: UPF consumption univariate association				
Lower tertile of UPF consumption	227	Reference	Reference	Reference
Middle tertile of UPF consumption	228	0.99 (0.60 - 1.63)	1.08 (0.65 - 1.79)	1.15 (0.69 - 1.93)
Higher tertile of UPF consumption	228	1.32 (0.83 - 2.21)	1.54 (0.95 - 2.50)	1.56 (0.92 - 2.62)
Model 2: Depression univariate association				
PHQ-9 summary score (< 6) Low	586	Reference	Reference	Reference
PHQ-9 summary score (>= 6) High	97	1.57 (0.95 - 2.59)	1.63 (0.98 - 2.71)	1.45 (0.84 - 2.51)
Model 3: Antidepressant use univariate association				
Anti-depressant use NO	625	Reference	Reference	Reference
Antidepressant use YES	58	1.54 (0.86 - 2.78)	1.57 (0.87 - 2.81)	1.61 (0.86 - 3.00)

UPF, Ultra-processed foods; PHQ-9, Patient Health Questionnaire-9.

*Fully adjusted model is adjusted for the following variables: age, sex, household income, education, ethnicity, born in Canada, smoking status, physical activity, daily alcohol consumption and BMI.

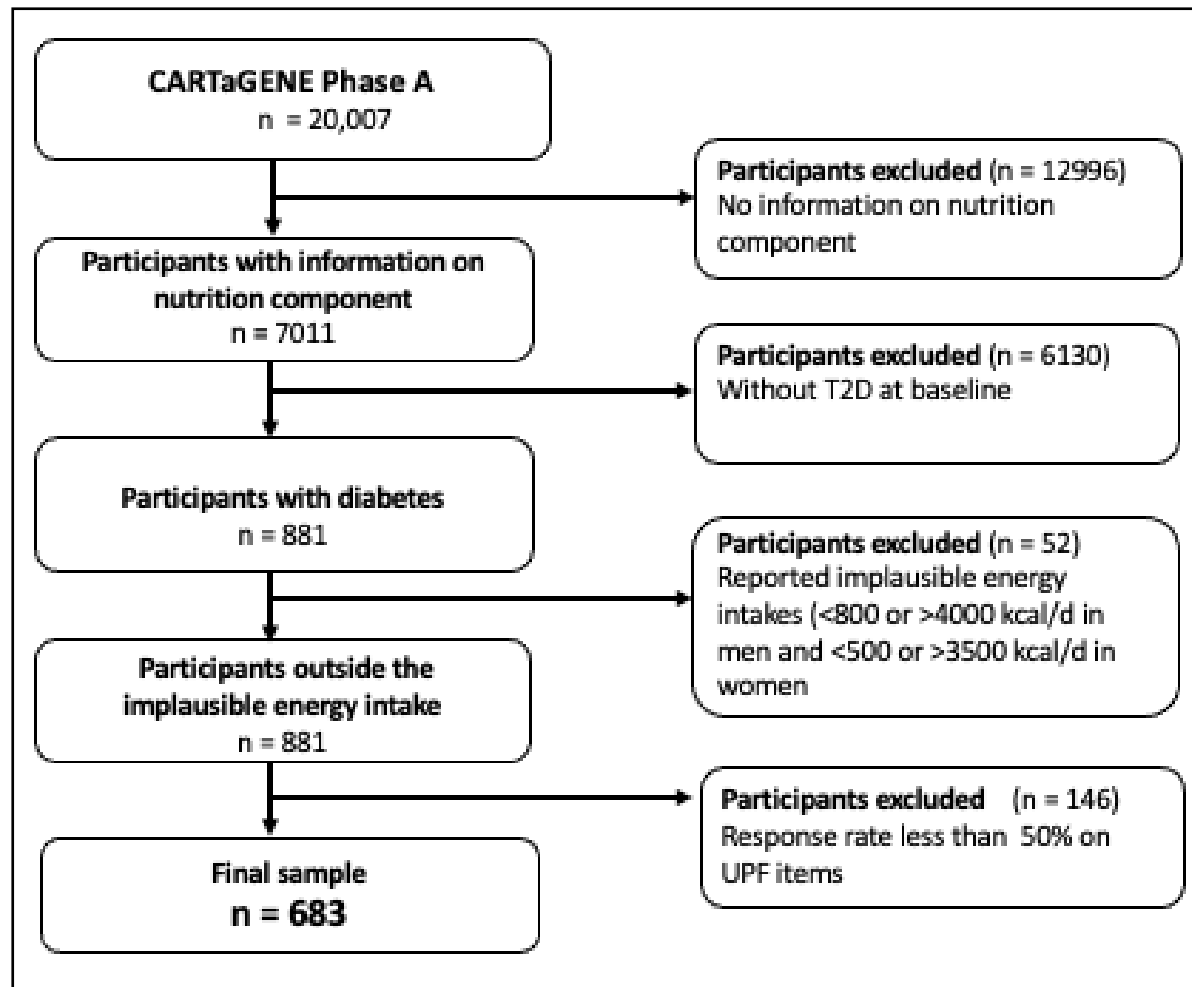
Table 4.4 Results of Cox regression for UPF consumption and depression assessed using PHQ-9 and antidepressant joint association for incident T2D complications

Groups	N	Incident complications (N)	Unadjusted Model, HR (95% CI)	Age- and Sex-Adjusted Model, HR (95% CI)	Fully Adjusted Model, HR (95% CI) *
Model 1 UPF consumption lower & middle tertile combined and depressive symptoms joint association					
LUND	395	52	Reference	Reference	Reference
LUD	60	10	1.49 (0.75 - 2.94)	1.48 (0.75 - 2.94)	1.39 (0.69 - 2.80)
HUND	191	34	1.29 (0.83 - 2.00)	1.40 (0.90 - 2.20)	1.41 (0.88 - 2.25)
HUD	37	9	2.07 (1.02 - 4.20)	2.43 (1.18 - 4.99)	2.07 (0.91 - 4.70)
Model 2 UPF consumption lower & middle tertile combined and depressive symptoms/Antidepressant use joint association					
LUNDA	367	49	Reference	Reference	Reference
LUDA	88	13	1.30 (0.70 - 2.42)	1.29 (0.70 - 2.40)	1.30 (0.69 - 2.45)
HUNDA	179	29	1.16 (0.73 - 1.84)	1.25 (0.78 - 2.01)	1.27 (0.78 - 2.09)
HUDA	49	14	2.37 (1.30 - 4.30)	2.82 (1.53 - 5.18)	2.59 (1.32 - 5.06)

*Fully adjusted model is adjusted for the following variables: age, sex, household income, education, ethnicity, born in Canada, smoking status, physical activity, daily alcohol consumption and BMI.

LUND, lower/middle tertile of ultra-processed foods consumption and low depressive symptoms; LUD, lower/middle tertile of ultra-processed foods consumption and high depressive symptoms; HUND, higher tertile of ultra-processed foods consumption and low depressive symptoms; HUD, higher tertile of ultra-processed foods consumption and high depressive symptoms; LUNDA, lower and middle tertile of ultra-processed foods consumption and low depressive symptoms and no antidepressant use; LUDA, lower and middle tertile of ultra-processed foods consumption and high depressive symptoms and antidepressant use; HUNDA, higher tertile of ultra-processed foods consumption and low depressive symptoms and no antidepressant; HUDA, higher tertile of ultra-processed foods consumption and high depressive symptoms or antidepressant.

Figure 4.1 Flow diagram of the final sample for the analysis



Supplementary Material for Chapter 4

Supplementary Table 4.1 Diabetes complication code

Diabetes complications	ICD-9 Diagnosis	ICD-9 codes (1,2,3)	ICD-10 Diagnosis	ICD-10 codes (4,5,6,7)
Microvascular				
Diabetic retinopathy	Diabetic ophthalmologic disease	250.5x		
	Background retinopathy	362.01		
	Other retinopathy	362.1	Diabetic retinopathy	H0-H4, H50-H53, H55, H57-H59, E103, E113, E143 E113, E143 or H360
	Retinal edema	362.83		
	Cystoid macular edema/degeneration (CSME)	362.53		
	Proliferative retinopathy	362.02		
	Retinal Detachment	361		
	Blindness	369	Vision loss or blindness on one or two eyes	H54
		362.81, 362.82		
	Other retinal disorders			
	Vitreous hemorrhage	379.23		
Nephropathy	Diabetic nephropathy	250.4	Diabetic nephropathy/ kidney disease	E11.2, E14.2 E11.7, E11.8, E14.7, E14.8, R809, N00-N08, N10-N19, N28.9
	Acute glomerulonephritis	580		
	Nephrotic syndrome	581		
	Chronic glomerulonephritis	582		
	Hypertension, nephrosis	581.81		
	Nephritis/nephropathy	583		
	Acute renal failure	584		N17

	Chronic renal failure	585		N18, N19
	Renal failure NOS	586		
	Renal insufficiency	593.9		
	Specified diabetic kidney disease	250.4	Specified diabetic kidney disease	E10.2, E11.2, E14.2
	Unspecified diabetic kidney disease	250.9	Unspecified diabetic kidney disease	E10.7, E10.8, E11.7, E11.8, E14.7, E14.8
Neuropathy	Diabetic neuropathy	356.9, 250.6	Diabetic neuropathy	E114, E115, E124, E125, E134, E135, E144, E145
	Amyotrophy	358.1		
	Cranial nerve palsy	951.0, 951.1, 951.3		
	Mononeuropathy	354.0-355.9		
	Charcot's arthropathy	713.5		
	Polyneuropathy	357.2		
	Neurogenic Bladder	596.54		
	Autonomic neuropathy	337.0, 337.1		
	Gastroparesis/diarrhea	564.5, 536.3		
	Orthostatic hypotension	458.0		
Macrovascular				
Cerebrovascular	TIA, Transient ischemic attack	435		
	Stroke	431, 433, 434, 436	Stroke	I61, I63–I67
Cardiovascular	Atherosclerosis	440.xx		

Peripheral vascular disease (PVD)	Other IHD (ischemic heart disease)	411, 415	Other (ischemic heart disease)	I24
	Angina pectoris	413	Angina pectoris	I20
	Other chronic IHD (ischemic heart disease)	414	Other chronic IHD	I25
	Myocardial infarction	410	Myocardial infarction	I21
	Ventricular fibrillation, arrest	427.1, 427.3	Subsequent myocardial infarction	I22
	Atrial fibrillation, arrest	427.4, 427.5	Certain current complications following acute myocardial infarction	I23
	Other ASCVD (atherosclerotic cardiovascular disease)	429.2		
	Old myocardial infarction	412		
	Heart failure	428	Heart failure	I46, I50, I11.0, I13.0, I13.2
	Atherosclerosis, severe	440.23, 440.24		
	Aortic aneurysm/dissection	441		
	Diabetic PVD	250.7		I70.2, I73.1, I73.9, I79.2, E10.5, E11.5, E14.5
	Other aneurysm, Lower extremity	442.3	Chronic arterial occlusion	I70
	peripheral vascular disease	443.81, 443.9		
	Foot wound + complication	892.1	Diabetic foot and ulcers	E11.6, E14.4, L00, L03, L08, L97
	Claudication, intermittent	443.9		

Embolism/thrombosis (LE)	444.22
Gangrene	785.4
Gas gangrene	0.40
Ulcer of lower limbs	707.1

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Supplementary Table 4.2 Results of cox regression for UPF consumption and depression assessed using PHQ-9 and anti-depressant joint association for type 2 diabetes microvascular complication incidence in CARTaGENE

Groups	N	Unadjusted Model, HR (95% CI)	Age- and Sex-Adjusted Model, HR (95% CI)	Fully Adjusted Model, HR (95% CI) *
Model 1 UPF consumption low/middle tertiles combined and depressive symptoms joint association				
LUND	295	Reference	Reference	Reference
LUD	60	1.34 (0.56 - 3.20)	1.34 (0.56 - 3.21)	1.20 (0.49 - 2.94)
HUND	191	1.46 (0.87 - 2.44)	1.60 (0.94 - 2.72)	1.57 (0.91 - 2.73)
HUD	37	2.80 (1.29 - 6.05)	3.33 (1.52 - 7.29)	2.64 (1.06 - 6.54)
Model 2 UPF consumption low/middle combined tertile and depressive symptoms/ Antidepressant use joint association				
LUNDA	362	Reference	Reference	Reference
LUDA	88	1.43 (0.70 - 2.92)	1.19 (0.54 - 2.60)	1.16 (0.52 - 2.56)
HUNDA	184	1.08 (0.61 - 1.89)	1.33 (0.75 - 2.35)	1.32 (0.73 - 2.38)
HUDA	49	2.71 (1.37 - 5.37)	4.06 (2.10 - 7.871)	3.67 (1.75 - 7.66)

LUND, lower/middle tertile of ultra-processed foods consumption and low depressive symptoms; LUD, lower/middle tertile of ultra-processed foods consumption and high depressive symptoms; HUND, higher tertile of ultra-processed foods consumption and low depressive symptoms; HUD, higher tertile of ultra-processed foods consumption and high depressive symptoms; LUNDA, lower and middle tertile of ultra-processed foods consumption and low depressive symptoms and no antidepressant use; LUDA, lower and middle tertile of ultra-processed foods consumption and high depressive symptoms or antidepressant use; HUNDA, higher tertile of ultra-processed foods consumption and low depressive symptoms and no antidepressant; HUDA, higher tertile of ultra-processed foods consumption and high depressive symptoms or antidepressant.

*Fully adjusted model is adjusted for the following variables: age, sex, household income, education, ethnicity, born in Canada, smoking status, physical activity, daily alcohol consumption and BMI.

We performed two sensitivity analyses, by performing the Cox regressions first with a 40% and second with a 60% response rate on the ultra-processed food and beverage items.

3. 40% response rate 15 questions out of 37 on UPF, sample size n = 814

Supplementary Table 4.3A Results of cox regression for UPF consumption and depression assessed using PHQ-9 and anti-depressant for type 2 diabetes combined complication incidence in CARTaGENE (40% response rate)

Groups	N	Unadjusted Model, HR (95% CI)	Age- and Sex-Adjusted Model, HR (95% CI)	Fully Adjusted Model, HR (95% CI) *
Model 1: UPF consumption univariate association				
Lower tertile of UPF consumption	271	Reference	Reference	Reference
Middle tertile of UPF consumption	272	0.90 (0.57 - 1.40)	0.93 (0.60 - 1.47)	0.96 (0.61 - 1.52)
Higher tertile of UPF consumption	271	1.20 (0.79 - 1.81)	1.31 (0.85 - 2.02)	1.28 (0.81 - 2.01)
Model 2: Depression univariate association				
PHQ-9 summary score (< 6) Low	697	Reference	Reference	Reference
PHQ-9 summary score (>= 6) High	117	1.68 (1.09 - 2.59)	1.77 (1.15 - 2.75)	1.63 (1.02 - 2.61)
Model 3: Anti-depressant use univariate association				
Anti-depressant use NO	745	Reference	Reference	Reference
Anti-depressant use YES	69	1.32 (0.76 - 2.30)	1.38 (0.79 - 2.42)	1.38 (0.77 - 2.49)

UPF, Ultra-processed foods; PHQ-9, Patient Health Questionnaire-9.

*Fully adjusted model is adjusted for the following variables: age, sex, household income, education, ethnicity, born in Canada, smoking status, physical activity, daily alcohol consumption and BMI.

Supplementary Table 4.3B Results of cox regression for UPF consumption and depression assessed using PHQ-9 and anti-depressant joint association for type 2 diabetes combined complication incidence in CARTaGENE (40% response rate)

Groups	N	Unadjusted Model, HR (95% CI)	Age- and Sex-Adjusted Model, HR (95% CI)	Fully Adjusted Model, HR (95% CI) *
Model 1 UPF consumption lower & middle tertile combined and depressive symptoms joint association				
LUND	472	Reference	Reference	Reference
LUD	71	1.56 (0.87 - 2.79)	1.60 (0.89 - 2.85)	1.53 (0.85 - 2.77)
HUND	225	1.20 (0.80 - 1.80)	1.27 (0.84 - 1.92)	1.25 (0.82 - 1.92)
HUD	46	2.14 (1.15 - 3.97)	2.50 (1.34 - 4.68)	2.22 (1.08 - 4.54)
Model 2 UPF consumption lower & middle tertile combined and depressive. symptoms/Antidepressant use joint association				
LUNDA	437	Reference	Reference	Reference
LUDA	106	1.23 (0.72 - 2.11)	1.27 (0.74 - 2.18)	1.27 (0.73 - 2.21)
HUNDA	212	1.07 (0.70 - 1.64)	1.24 (0.73 - 1.74)	1.13 (0.72 - 1.76)
HUDA	59	2.29 (1.33 - 3.92)	2.72 (1.57 - 4.71)	2.50 (1.36 - 4.58)

LUND, lower/middle tertile of ultra-processed foods consumption and low depressive symptoms; LUD, lower/middle tertile of ultra-processed foods consumption and high depressive symptoms; HUND, higher tertile of ultra-processed foods consumption and low depressive symptoms; HUD, higher tertile of ultra-processed foods consumption and high depressive symptoms; LUNDA, lower and middle tertile of ultra-processed foods consumption and low depressive symptoms and no antidepressant use; LUDA, lower and middle tertile of ultra-processed foods consumption and high depressive symptoms or antidepressant use; HUNDA, higher tertile of ultra-processed foods consumption and low depressive symptoms and no antidepressant; HUDA, higher tertile of ultra-processed foods consumption and high depressive symptoms or antidepressant.

*Fully adjusted model is adjusted for the following variables: age, sex, household income, education, ethnicity, born in Canada, smoking status, physical activity, daily alcohol consumption and BMI.

4. 60% response rate 22 questions out of 37 on UPF, sample size n = 561

Supplementary Table 4.4A Results of cox regression for UPF consumption and depression assessed using PHQ-9 and anti-depressant for type 2 diabetes combined complication incidence in CARTaGENE (60% response rate)

Groups	N	Unadjusted Model, HR (95% CI)	Age- and Sex-Adjusted Model, HR (95% CI)	Fully Adjusted Model, HR (95% CI) *
Model 1: UPF consumption univariate association				
Lower tertile of UPF consumption	187	Reference	Reference	Reference
Middle tertile of UPF consumption	187	0.94 (0.55 - 1.61)	1.06 (0.61 - 1.81)	1.10 (0.63 - 1.93)
Higher tertile of UPF consumption	187	1.35 (0.82 - 2.21)	1.56 (0.93 - 2.62)	1.55 (0.89 - 2.71)
Model 2: Depression univariate association				
PHQ-9 summary score (< 6) Low	697	Reference	Reference	Reference
PHQ-9 summary score (>= 6) High	117	1.48 (0.88 - 2.49)	1.57 (0.93 - 2.66)	1.40 (0.80 - 2.47)
Model 3: Antidepressant use univariate association				
Anti-depressant use NO	745	Reference	Reference	Reference
Anti-depressant use YES	69	1.71 (0.95 - 3.09)	1.69 (0.93 - 3.05)	1.70 (0.91 - 3.21)

UPF, Ultra-processed foods; PHQ-9, Patient Health Questionnaire-9.

*Fully adjusted model is adjusted for the following variables: age, sex, household income, education, ethnicity, born in Canada, smoking status, physical activity, daily alcohol consumption and BMI.

Supplementary Table 4.4B Results of cox regression for UPF consumption and depression assessed using PHQ-9 and anti-depressant joint association for type 2 diabetes combined complication incidence in CARTaGENE (60% response rate)

Groups	N	Unadjusted Model, HR (95% CI)	Age- and Sex- Adjusted Model, HR (95% CI)	Fully Adjusted Model, HR (95% CI) *
Model 1 UPF consumption lower & middle tertile combined and depressive symptoms joint association				
LUND	318	Reference	Reference	Reference
LUD	56	1.27 (0.62 - 2.60)	1.30 (0.63 - 2.67)	1.21 (0.58 - 2.53)
HUND	158	1.30 (0.81 - 2.07)	1.39 (0.86 - 2.25)	1.37 (0.83 - 2.27)
HUD	29	2.26 (1.10 - 4.64)	2.65 (1.28 - 5.49)	2.42 (1.05 - 5.55)
Model 2 UPF consumption lower & middle tertile combined and depressive symptoms/Antidepressant use joint association				
LUNDA	295	Reference	Reference	Reference
LUDA	79	1.25 (0.65 - 2.38)	1.25 (0.65 - 2.40)	1.22 (0.63 - 2.36)
HUNDA	147	1.14 (0.69 - 1.89)	1.21 (0.73 - 2.03)	1.21 (0.70 - 2.06)
HUDA	40	2.72 (1.48 - 5.01)	3.14 (1.69 - 5.82)	3.00 (1.53 - 5.91)

LUND, lower/middle tertile of ultra-processed foods consumption and low depressive symptoms; LUD, lower/middle tertile of ultra-processed foods consumption and high depressive symptoms; HUND, higher tertile of ultra-processed foods consumption and low depressive symptoms; HUD, higher tertile of ultra-processed foods consumption and high depressive symptoms; LUNDA, lower and middle tertile of ultra-processed foods consumption and low depressive symptoms and no antidepressant use; LUDA, lower and middle tertile of ultra-processed foods consumption and high depressive symptoms or antidepressant use; HUNDA, higher tertile of ultra-processed foods consumption and low depressive symptoms and no antidepressant; HUDA, higher tertile of ultra-processed foods consumption and high depressive symptoms or antidepressant.

*Fully adjusted model is adjusted for the following variables: age, sex, household income, education, ethnicity, born in Canada, smoking status, physical activity, daily alcohol consumption and BMI.

Bridge Statement 2

Results from the first and second manuscripts showed that individuals with depression and who are high UPF consumers might be at a higher risk for T2D and its complication. Thus, reducing UPF consumption might be an important step to consider when addressing the relationship between depression and T2D. However, it is not clear how much UPF consumption contributes to the relationship between depression and T2D incidence. Thus, the third manuscript aimed to empirically explore such relationship.

Chapter 5: Manuscript 3. The mediating role of ultra-processed foods consumption in the association between depression and type 2 diabetes incidence: Results from a prospective cohort study

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Abstract

Objectives: This study investigated ultra-processed food (UPF) consumption and body mass index (BMI) as potential mediators of the association between depression and type 2 diabetes (T2D) incidence.

Methods: A total of $N = 3880$ respondents from the CARTaGENE community cohort study in Quebec were included in the study. Food and drink consumption was assessed using a validated questionnaire and UPF were categorized using NOVA classification system. BMI was based on measured body weight and height at baseline. Depression was measured from the administrative health database five years before the baseline. Survey data were linked with diagnostic codes from a public insurance database to examine incident T2D during a seven-year follow-up period. Mediation analyses examined the direct, indirect, and total effects of depression on T2D incidence and the specific indirect effects of depression on T2D incidence through UPF consumption and BMI.

Results: Depression positively predicted UPF consumption at the baseline ($b = 0.048$, $s.e. = 0.016$, $p < 0.01$), which in turn was a positive predictor of T2D incidence ($b = 0.100$, $s.e. = 0.035$, $p < 0.01$). In the second mediation model, depression remained a significant positive predictor of UPF consumption ($b = 0.050$, $s.e. = 0.016$, $p < 0.01$) and was also a significant positive predictor of BMI at baseline ($b = 0.050$, $s.e. = 0.017$, $p < 0.01$). UPF consumption was a significant positive predictor of T2D incidence ($b = 0.096$, $s.e. = 0.034$, $p < 0.01$). Moreover, BMI was also a positive predictor of T2D incidence ($b = 0.282$, $s.e. = 0.028$, $p < 0.001$). In a fully adjusted parallel dual mediation model, the indirect effect of depression on T2D through potential mediators UPF consumption and BMI was 0.033 ($p < 0.01$) and 0.096 ($p < 0.01$), respectively.

Conclusion: These results suggest that depression may partly be related to T2D incidence via UPF consumption and BMI. Intervention programs targeting these mediators of the association between depression and T2D could become a promising strategy for reducing T2D.

Keywords: Ultra-processed food, Depressive symptoms, Type 2, Mediation,

Introduction

Type 2 diabetes mellitus (T2D) is an increasingly prevalent health condition that significantly impacts the quality of life of millions of people worldwide (1). The co-occurrence of biological, psychological, and psychosocial issues can be essential in managing diabetes mellitus (1). A growing amount of evidence supports a strong and independent relationship between psychosocial stressors and the development of T2D (2), especially depression (3). Depression is a serious mood disorder that is not only commonly comorbid with T2D but is also a modifiable risk factor for T2D morbidity and mortality (4). Specifically, several epidemiologic studies have suggested a significant association between depression and the incidence of T2D (5). A meta-analysis showed that individuals with depression increase the risk of T2D incidence by 40–60% (4).

Although the mechanisms linking depression and T2D are poorly understood, several hypotheses have been proposed. First, systemic inflammation is an emerging risk factor for depression that is also independently associated with the risk of T2D (6). Studies have shown that individuals with depression may have higher levels of inflammatory biomarkers, which can lead to insulin resistance and an increased risk of developing T2D (6, 7). Moreover, this association may be mediated by lifestyle-related behaviors, such as consuming unhealthy diets and decreased physical activity (7), which could represent clinically relevant targets for preventive interventions.

Second, unhealthy diets, high in ultra-processed foods (UPF), which are a growing part of the world's food supply (8), are an important risk factor for the development of T2D (9). Various classification systems have been developed to classify food and drink based on levels of processing with the NOVA classification (not an acronym) the most common and popular

system used to divide food and drinks based on the nature, extent, and purpose of food processing (10).

The NOVA classification comprises four categories: (1) unprocessed or minimally processed food (e.g., fresh vegetables/fruits, unprocessed meat); (2) processed culinary ingredients (e.g., butter/oil for cooking, sugar, salt); (3) processed food (e.g., canned vegetables/fish, fruits in syrup); and (4) ultra-processed food (e.g., processed meat, soft drinks) (9). NOVA defines UPF as formulations of industrial ingredients that result from a series of industrial processes (hence ‘ultra-processed’) (11). The commonly resulting food products are ready to eat, have little or no whole food content, are hyper-palatable, and prevent the proliferation of micro-organisms that are so necessary for human health (11).

A recent meta-analysis has shown that the risk of T2D among high UPF consumers was 31% higher compared to low UPF consumers (9). Eating such unhealthy diets is also common among individuals with depression. To illustrate, studies have reported that individuals with depression present excessive energy intake and exhibit higher sugar and fat consumption compared to non-depressed individuals (12). The Whitehall II cohort study has shown that individuals who consumed higher amounts of UPF had a 31% higher risk of developing depression than individuals who consumed lower amounts of UPF (13).

Taken together, it is possible that UPF may mediate the relationship between depression and T2D. One of the pathways by which UPF could link depression and T2D might be through inflammation pathways. For example, high UPF consumption is associated with inflammatory markers such as C-reactive protein, TNF- α , IL-1, and IL-6 levels, despite controlling for the other dietary and lifestyle factors (14). Further, UPF consumption is also associated with obesity (15), a well-established risk factor for T2D (16). However, findings from prospective studies

indicate that the consumption of UPF may elevate the risk of T2D independently of factors such as BMI and other known diabetes risk factors (17). Also, individuals with depression are involved in increased caloric consumption (12), which can increase body weight (18) and substantially increase the risk of T2D (7).

Although a reduction in UPF consumption might be one of the crucial targets for preventive interventions for T2D, the contribution of UPF to the association between depression and T2D is poorly understood. It remains unclear the extent to which UPF consumption may explain the link between depression and T2D. Such understanding is needed to help guide preventive measures aimed at reducing the risk of T2D among individuals with depression. Although prior research has linked depression and T2D incidence (7), the potential role of UPF consumption in the depression to T2D incidence pathways has, to our knowledge, not yet been explored.

To address the current knowledge gap, this study aims to estimate the extent to which UPF consumption contributes to the relationship between depression and T2D incidence. We hypothesized that (i) depression will be associated with T2D and (ii) ultra-processed consumption will be a substantial mediating factor between depression and T2D. Moreover, as discussed above, UPF consumption has been identified as a potential risk factor for the development of T2D (13). Notably, this association persists even when controlling for body mass index (BMI) (13), which itself is a robust predictor of T2D (13). Consequently, our study aims to investigate the extent of mediation that may occur with UPF in the presence of BMI as a second mediator.

Methods

Study sample

Data from a large population health survey and an administrative health database were linked to create the sample for the present study representing our analysis of secondary data. Respectively, baseline data were from the CARTaGENE health survey (2009–2010), which was conducted in the Canadian province of Quebec in the adult population aged 40–69 years (19). Respondents were randomly recruited from the public health insurance database called the Régie de l'assurance maladie du Québec (RAMQ). Most residents of Quebec have health coverage under this government health insurance plan.

By way of background, recruitment into CARTaGENE baseline consisted of two phases. Phase A was conducted from 2009 to 2010, and phase B was conducted from 2012 to 2015 (17). The present study consisted of secondary analyses of phase A data on UPF consumption, depression, and the risk of T2D, which linked CARTaGENE survey data and the RAMQ billing code data. A total of 20,007 adults between the ages of 40 and 69 years without T2D at baseline (phase A) participated in CARTaGENE. However, only respondents with information on the nutrition component at baseline were included ($n = 7011$) in our sampling protocol. In addition, respondents were excluded if they reported unlikely energy intakes below 800 kcal/d or above 4000 kcal/d in men and below 500 kcal/d or above 3500 kcal/d in women ($n = 1240$). Further, (a) respondents who reported diabetes at baseline based on a positive response to the following question: “Has a doctor ever told you that you had diabetes?” ($n = 326$), and (b) those whose data could not be linked to the provincial health insurance database ($n = 3$) were also excluded. Finally, respondents whose response rates were less than 50 % on the UPF items ($n = 1562$) were excluded (how UPF consumption was calculated as described later in this section). A total of $N =$

3880 respondents comprised the sample frame for the secondary analyses conducted in this paper. Figure 5.1 depicts the sample selection procedure.

Respondents provided informed consent before participation and agreed to have their data linked with hospital and diagnostic information from the RAMQ database (19). The Douglas Mental Health University Institute Research Ethics Board and the St. Justine Hospital Research Ethics Board approved the study. Details of the study procedures have been published elsewhere (19).

Measures

Assessment of depression

Depression was assessed by an inpatient or outpatient diagnosis based on the administrative health database five years before the CARTaGENE baseline (2009–2010) assessment. Diagnostic codes for depression in the RAMQ database were examined and included the following ICD-9 codes: 296.2 (major depressive disorder single episode); 296.3 (major depressive disorder recurrent episode); 298.0 (depressive type psychosis); 300.4 (dysthymic disorder); 309.0 (adjustment disorder with depressed mood); 309.1 (prolonged depressive reaction); 311 (depressive disorder, not elsewhere classified); ICD-10 codes F32 (depressive episode); F33 (recurrent depressive disorder); and F34 (persistent mood disorders). Diagnostic codes for depression were considered when one diagnostic code was present within a one-year period during the last five years before the survey baseline.

Dietary assessment

At baseline, dietary consumption was assessed using the validated *Canadian-adapted Diet History Questionnaire II* (C-DHQ II), which was designed to assess food consumption over the previous 12 months. First, the questionnaire assessed the frequency of consumption and

portion sizes. Frequency of consumption of the items was converted into daily equivalents such as never = 0; 1–6/year = 0·01; 7–11/year = 0·02; 1/month = 0·03; 2–3/month = 0·07; 1/week = 0·14; 2/week = 0·29; 3–4/week = 0·48; 5–6/week = 0·74; 1/day = 1; 2 days or more = 3 as specified by the C-DHQII database (20). Second, a nutrient database for the C-DHQII was used to convert the portions of consumed food items into grams (20).

Portions are sex-specific and based on the percentiles of intake reported in the *Canadian Community Health Survey – Cycle 2.2 Nutrition* (21). The consumed amount for every food item was then calculated by multiplying the frequency per day and grams of consumption. Food items such as vitamins, minerals, or herbal supplements without portion size were excluded from the present analysis. Zero imputation was used to deal with missing data. More details about procedures have been published elsewhere (22).

To estimate the daily dietary intake of UPF consumption (g/d) based on NOVA food group classification, we summed the amount consumed (g/d) of each food and beverage item classified as UPF group (a total of 30 foods and seven beverage items). Further, log transformation was performed on the UPF group (continuous) to deal with non-normal or skewed data (23).

Incidence of T2D

Diabetes diagnosis during the seven-year follow-up period was measured with the RAMQ billing database up to December 31, 2016. In addition, the date of first diagnostic codes or hospital admission using the following diagnostic code were recorded: ICD-9 code 250, and ICD-10 code E11.

Control variables

Analyses were adjusted for (a) sociodemographic variables including age, sex, marital status, education, annual household income, and country of birth; (b) behavioral variables including smoking status, alcohol consumption, and physical activity; (c) BMI; and (d) hemoglobin HbA1c status. All variables were captured at the CARTaGENE baseline assessment.

Statistical analysis

Descriptive statistics, including means, standard deviations, and frequencies, were performed to assess the characteristics of the sample by the presence or absence of T2D. Logistic regression was performed to investigate the independent association of depression and UPF consumption on T2D incidence, computing odds-ratio (OR) and 95% confidence interval (CI) before and after adjusting for covariates.

Statistical mediation was examined by path analysis. This statistical technique used in structural equation modeling (SEM) to examine the relationships between observed variables and latent constructs (24). Path analysis is a statistical technique utilized within SEM to explore a closed system of nested relationships among variables. This method is expressed mathematically through a series of structured linear regression equations, offering insights into both direct and indirect associations among observed and latent variables (24).

Path analysis was used to estimate the direct, indirect, and total effects of depression on T2D incidence and the specific indirect effects of depression on T2D incidence through mediators (UPF consumption and BMI) using standardized regression coefficients. Direct effects represent the direct association between depression and T2D incidence that is not mediated by UPF consumption; indirect effects are the indirect association of depression on T2D incidence via the pathway of UPF consumption. The total effect comprises both direct and indirect effects (24).

Two mediation models were conducted. First, a single mediator model was conducted to test the indirect effect of depression on T2D through UPF consumption. Second, a parallel dual-process mediation model was conducted to estimate the indirect effects of depression on T2D via UPF consumption and BMI. Mediation models controlled for the above-described variables. Path analyses were conducted using MPlus 8.9 software. All other statistical analyses were carried out with SPSS version 27. Statistical significance was evaluated with α set a priori at 0.05.

Results

Sample characteristics

Table 5.1 presents the characteristics of study respondents by presence or absence of T2D incidence. Respondents who developed T2D during the seven-year follow-up period were more likely to be older, more educated, and in the middle-income level group at baseline. Further, these respondents also reported a higher BMI of 30.4(6.0) and higher UPF consumption 307(414.9) g/d at baseline. There were 37 food items identified in the UPF group; overall mean UPF consumption was 225.8 g/d (SD 331.8). The mean follow-up time period for this sample was 2334 days (6.4 years).

Regression and mediation analyses

Depression diagnosis before the CARTaGENE baseline and UPF consumption at the CARTaGENE baseline were both predictors of T2D onset. In the logistic regression, the OR (95% CI) for the association between depression and T2D incidence was 1.86 (1.29 -2.68) in model adjusted for age and sex and was 1.58 (1.05 - 2.36) after controlling for the potential covariates. Further, the OR (95% CI) for the association between UPF consumption and T2D

incidence was 2.23 (1.58 - 3.14) in model adjusted for age and sex and was 1.72 (1.18-2.51) after controlling for the potential covariates.

Standardized path coefficients are reported for all mediation analyses. In the single mediation model (Figure 5.2a shows the model adjusted for age and sex, and Figure 5.2b shows the fully adjusted model), the indirect effect of depression diagnosis on T2D incidence via UPF consumption was statistically significant. The overall path model was adjusted for age, sex, educational level, marital status, income, country of birth, physical activity, smoking status, alcohol consumption, Hba1c levels, and BMI. The standardized indirect effect of depression diagnosis on T2D incidence via the potential mediator UPF consumption was 0.005 and statistically significant ($p < 0.05$) in the fully adjusted model as well as model adjusted for age and sex (indirect effect = 0.048, $p < 0.01$).

Depression diagnosis in the last five years previous to the baseline survey was found to be a significant positive predictor of UPF consumption at the baseline in the model adjusted for age and sex ($b=0.050$, $s.e.=0.015$, $p<0.001$) and showed to be positive predictor in the fully adjusted model ($b = 0.048$, $s.e. = 0.016$, $p < 0.01$). UPF consumption at the survey baseline was, in turn, a significant positive predictor of T2D incidence ($b=0.149$, $s.e. = 0.033$, $p<0.001$, model adjusted for age and sex; $b = 0.100$, $s.e. = 0.035$, $p < 0.0$, fully adjusted model). Further, depression was a significant direct positive predictor of the T2D incidence in model adjusted for age and sex ($b=0.089$, $p<0.01$) and in the fully adjusted model ($b = 0.067$, $p < 0.05$). In the fully adjusted model, the total effect of depression on T2D incidence was 0.072. The ratio of total indirect effects (mediated through UPF consumption) / total effect (i.e., the effect of depression on T2D incidence that is mediated through UPF consumption) was $0.005/0.072 = 7\%$. In other words, 7% of the association between depression and T2D incidence was explained by UPF

consumption in fully adjusted model which was similar to the model adjusted for age and sex (7.2%), whereas 93% was explained from a direct association between depression and T2D incidence in a single mediation model.

In the second mediation model, both UPF consumption and BMI were used as parallel potential mediators with age, sex, educational level, marital status, income, country of birth, physical activity, smoking status, alcohol consumption, and Hba1c levels as covariates. Figure 5.3a illustrates results for the model adjusted for age and sex, and Figure 5.3 b illustrates results for the fully adjusted model. Depression diagnosis was a significant positive predictor of UPF consumption at baseline for the model adjusted for age and sex ($b = 0.050$, $s.e. = 0.015$, $p < 0.01$), in addition to the fully adjusted model ($b = 0.048$, $s.e = 0.016$, $p < 0.01$). Further, depression was also a significant positive predictor of BMI at baseline for age and sex model (0.041 , $s.e. = 0.016$, $p < 0.01$) and for the fully adjusted model ($b = 0.050$, $s.e = 0.017$, $p < 0.01$). UPF consumption was a significant positive predictor of T2D incidence ($b = 0.087$, $s.e. = 0.033$, $p < 0.01$, model adjusted for sex and age; $b = 0.010$, $s.e = 0.034$, $p < 0.0$, fully adjusted model). Moreover, BMI was also a positive predictor of T2D incidence ($b = 0.284$, $s.e. = 0.026$, $p < 0.001$, model adjusted for sex and age; $b = 0.282$, $s.e = 0.028$, $p < 0.001$, fully adjusted model). The standardized indirect effect of depression on T2D via potential mediator UPF consumption was 0.033 ($p < 0.01$) in fully adjusted model. The indirect effect in the model adjusted for age and sex was 0.004 ($p < 0.05$). The standardized indirect effect of depression on T2D via potential mediator BMI was 0.096 ($p < 0.01$) in the fully adjusted model, and the indirect effect in the model adjusted for age and sex was 0.012 and was also statistically significant ($p < 0.05$). Further, depression was a significant direct positive predictor of the T2D incidence ($b = 0.076$, $p < 0.01$ model adjusted for age and sex; $b = 0.067$, $p < 0.05$, fully adjusted model). In the parallel mediation model, the total

effect of depression on T2D incidence was 0.196. The ratio of total indirect effects (mediated through UPF consumption) / total effect (i.e., the effect of depression on T2D incidence that is mediated through UPF consumption) was $0.033/0.196 = 0.17$, suggesting that in fully adjusted model 17% of the association between depression and T2D incidence was explained by UPF consumption which was very similar to model adjusted for age and sex (17.4%).

Discussion

The present study investigated UPF consumption as a potential mediator of the association between depression and T2D incidence among older adults living in Quebec, Canada. We further examined if UPF consumption remained a mediator if we considered BMI as a parallel mediator. Consistent with our hypotheses, we found that a retrospectively reported depression diagnosis was associated with a higher risk of T2D. Further, UPF consumption at baseline, might be one of the mechanisms linking depression and T2D, the mediating effect of UPF consumption was statistically significant but weak. We also found a statistically significant mediating effect of UPF consumption when considering a potential role of BMI on the association between depression and T2D onset.

Consistent with prior literature, our result that depression increased the risk of T2D was supported by epidemiological studies. Various meta-analyses have reported depression and its relationship to T2D (23, 25). For instance, Yu et al. found that the relative risk (RR) for T2D was 1.32 (1.18 - 1.47) (23). Further, a recent meta-analysis, combining all measures of depression, such as depressive symptom scales, clinical interviews, physician diagnoses, and use of antidepressants, revealed that the RR for incident diabetes was 1.18 (1.12 - 1.24) (25).

The present study is one of the first population-based studies to examine the association between depression and the risk of T2D mediated by UPF consumption. To our knowledge,

previous studies have examined these associations only indirectly. One study (26) assessed how diet and physical activity could contribute to the relationship between depression and metabolic syndrome. Its results suggested that 23% of the effect of depression on the risk of metabolic syndrome was mediated through diet and physical activity (26, 25). Another study (27) reported that (a) depressive symptoms at baseline were associated with glycemic control five years later, and (b) health behaviors (e.g., physical exercise, body weight control, and current smoking status) accounted for 13% of the association between depressive symptoms and HbA1c levels (27).

In the present study, we found that past depression was positively associated with UPF consumption and BMI at baseline, which in turn were positively associated with the T2D risk. Depression is associated with lifestyle factors such as increased consumption of energy intake, sugar, and fat, which can increase the risk of obesity and T2D. Depression might influence appetite and food choices by people preferring an unhealthy diet through changes in brain functioning (28). One explanation is that individuals with depression may prefer eating high-fat-high-sugar food to ameliorate unpleasant affective states through the stimulation of the reward system (29).

Further, an individual with depression has been shown to be more sedentary and involved in a less active lifestyle than their counterparts (30). Physical inactivity has simultaneous effects on weight gain (31) and increases the risk of inflammatory responses (32), which are recognized risk factors for T2D. Researchers have reported no significant association observed between depression and risk of diabetes when BMI and physical activity were adjusted. This implies that BMI and physical inactivity might be one of the pathways that contribute to the association discussed above (4).

While UPF consumption and BMI pathways could play a role in the association between depression and T2D risk, alternative mechanisms may also be involved in this relationship. To illustrate, depression may influence T2D risk through biological pathways such as increased activity in the hypothalamic–pituitary–adrenal (HPA) axis and inflammation (7, 33). The chronic and acute depressed state can increase the level of cortisol, which in turn leads to increased glycogenolysis and insulin resistance and gradually increase the risk of T2D (7). Inflammatory markers, such as pro-inflammatory cytokines, notably interleukin-6 (IL-6) and TNF α , are associated with depression (34). Inflammation is suggested to play a crucial role in the pathogenesis of T2D (14) and, therefore, may provide a mechanism between depression and incremental increases in glucose levels. Finally, some medications used in the treatment of depression (e.g., atypical antipsychotics) can increase the risk of weight gain, which can contribute to the development of T2D (5). One meta-analysis reported that the use of antidepressant drugs was associated 68% risk of diabetes (5).

Study strengths and limitations

Our study had several strengths. This was a large, prospective cohort study of middle-aged adults without T2D at the start of the study and followed for up to seven years, linking survey data with administrative data. One strength of our study was the use of billing codes to assess the incidence of T2D. Further, the temporal research design is considered a major strength when conducting a mediation analysis.

An important study limitation is that we excluded individuals with self-reported diabetes and those who were not on the clinical measures at the baseline to study the role of depression in the onset of diabetes; thus, we cannot rule out the possibility of reverse causality (i.e., a different

association than expected). It is possible that respondents in the early stages of diabetes were not captured at the baseline.

The diagnostic code use for depression was based on a single claim. We did not have the ability to differentiate between depression and more general psychological distress. It is possible that individuals with some health issues had more frequent visits to healthcare professionals and, therefore, were more likely to have a diagnostic code for depression in the RAMQ database. Although diabetes surveillance systems in Canada use at least one hospitalisation record or at least two physician claims in a two-year period, we choose the single claim to diagnose the diabetes cases because of our limited follow-up time.

Finally, dietary intake data measured using C-DHQ II at baseline were assessed by self-report, which may be subjected to respondents' reporting bias. Further, C-DHQ II used in this study was designed to assess the intake of major food groups, energy, and macronutrients, but not the intake of UPF in particular.

Conclusion

Using longitudinal data and mediation analysis, this study found that depression was associated with a greater risk of T2D, and 7% of this association may be mediated by UPF consumption. Furthermore, when BMI was considered as a parallel mediator, UPF consumption remained a mediating factor.

T2D is a complex, chronic disease that is not attributable to solely consuming a poor diet such as UPF but rather follows a pathway through longer-term depression and UPF consumption, which represents a more proximal health behavior. Our study thus provides a basis for further evaluating other unexamined mediators in the link between depression and T2D.

Results support our conclusion that researchers and practitioners should put emphasis on reducing the consumption of UPF and maintaining a healthy body weight (BMI) to prevent T2D in the presence of depression. Intervention programs targeting these mediators of the association between depression and T2D could become a promising strategy for reducing T2D.

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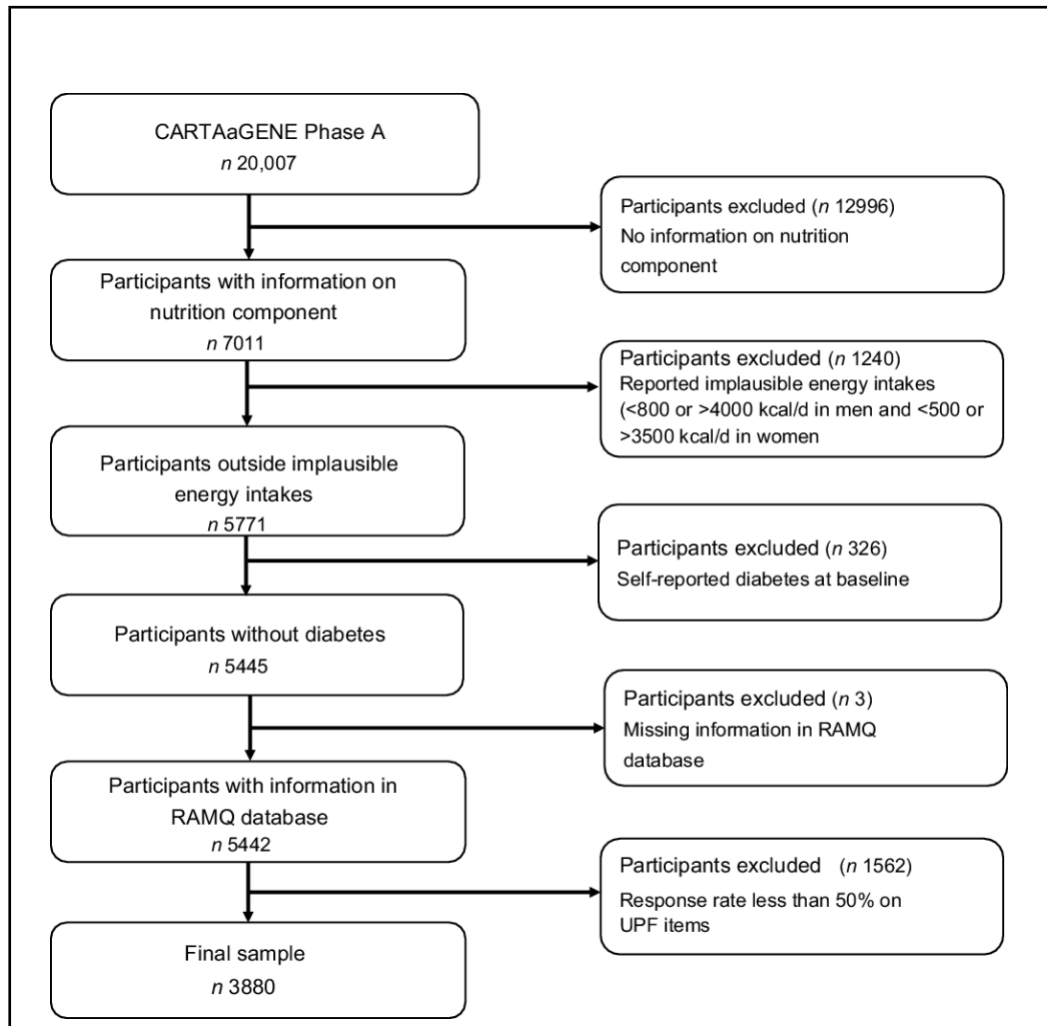
Table 5.1 Participants' characteristics according to type 2 diabetes status

	No Type 2 Diabetes (n = 3617)	Type 2 Diabetes (n = 263)	P -value ¹
Sociodemographic variables			
Age (years), mean $\pm$ SD	54.0 $\pm$ 7.5	57.2 $\pm$ 7.6	0.35
Sex, N (%)			< 0.0001
Male	1419 (39.2%)	137 (52.1 %)	
Female	2198 (60.8 %)	126 (47.9 %)	
Post-secondary education			<0.001
No	763 (21.1 %)	83 (31.6%)	
Yes	2854 (79.9%)	180 (68.4%)	
Household income N			0.024
Lower income level <49,999	1026 (28.4 %)	80 (30.4%)	
Medium income level (50,00 - 149,999)	2190 (60.5%)	168 (63.9%)	
High income level >150,000	401(11.1%)	15 (3.5%)	
Marital Status			0.154
Married/Partner	2421 (66.9%)	174 (66.2%)	
Single	499 (13.8%)	28 (10.6%)	
Divorced/Separated/widow	697 (19.3%)	61 (23.2%)	
Born in Canada			0.515
No	367 (10.1%)	30 (11.4%)	
Yes	3250 (89.9%)	233 (88.6%)	
Lifestyle and behavioral			
Physical			0.289
No	1426 (39.4%)	95 (36.1%)	
Yes	2191 (60.6%)	168 (63.9%)	
Smoking Status			0.004
Daily and occasional	539 (14.9)	42 (16.0%)	
Past smoking	1466 (40.5%)	131 (49.8%)	
Never smoking	1612 (44.6%)	90 (34.2%)	
Daily alcohol consumption			0.771
No	3185 (88.1%)	230 (87.5%)	
Yes	432 (11.9%)	33 (12.5%)	
BMI (kg/m ²)	26.7 $\pm$ 4.8	30.4 $\pm$ 6.0	< 0.0001
UPF consumption (g/d)	219. 8 $\pm$ 324.2	307.6 $\pm$ (414.9)	< 0.0001

Results reported as mean $\pm$ SD for continuous data and n (%) for categorical data.

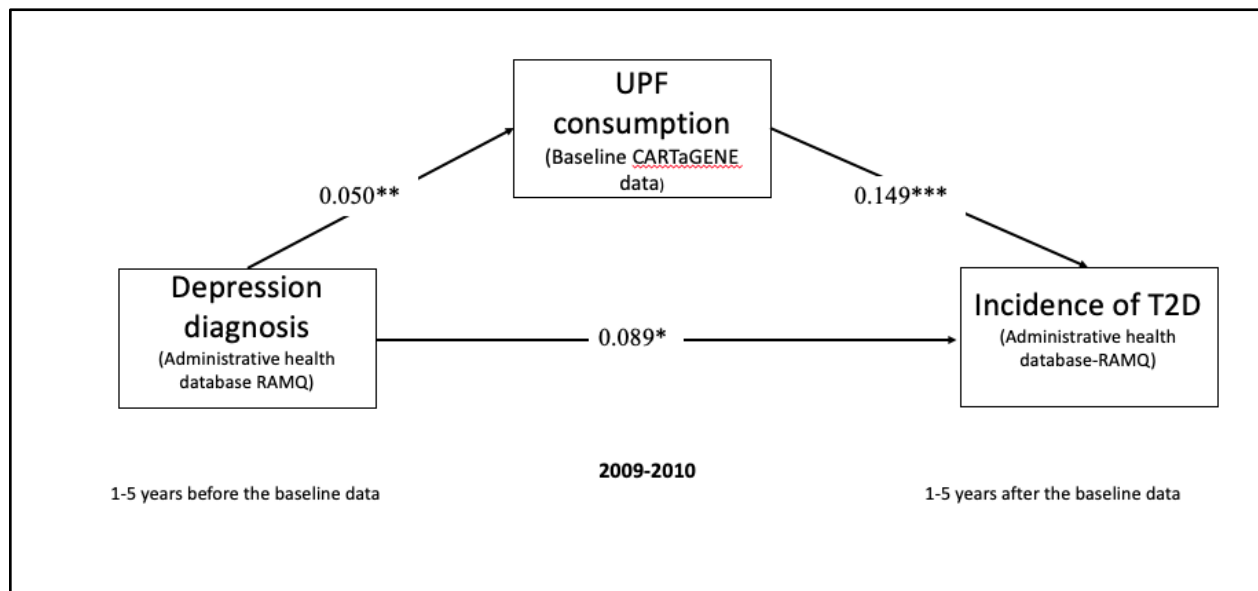
¹Chi-square tests for independence and independent sample t-tests were performed to determine whether any significant differences between individuals with type 2 diabetes and individuals with diabetes.

Figure 5.1 Flow diagram of the final sample for the analysis



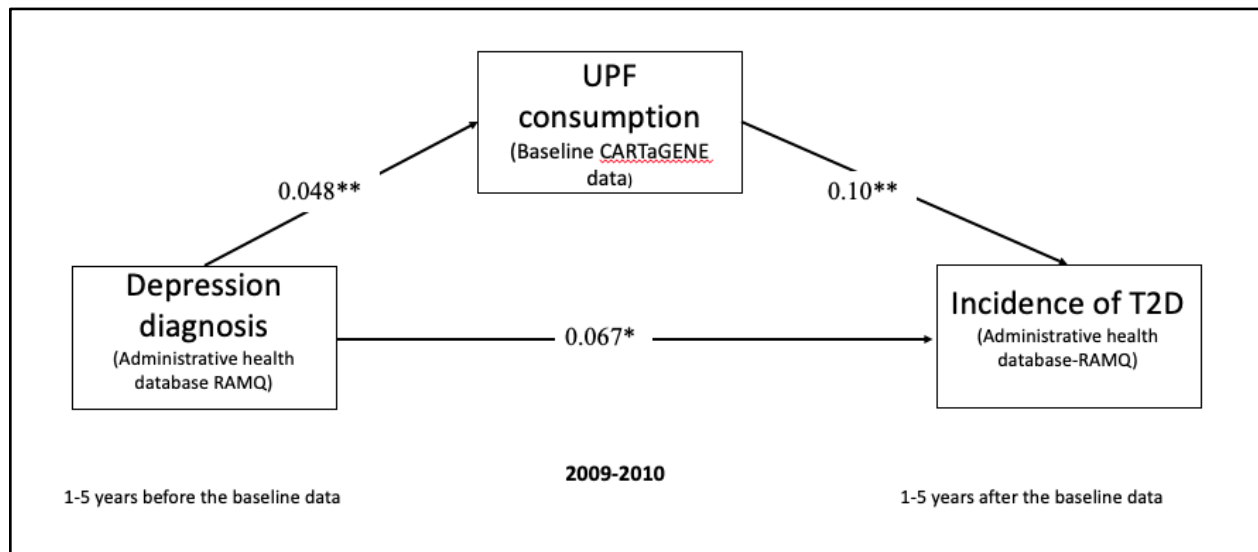
RAMQ, Régie de l'Assurance Maladie du Québec; UPF, Ultra-processed foods

Figure 5.2a Results of single mediation model testing whether the effect depression on type 2 diabetes was mediated by ultra-processed food consumption in model adjusted for age and sex



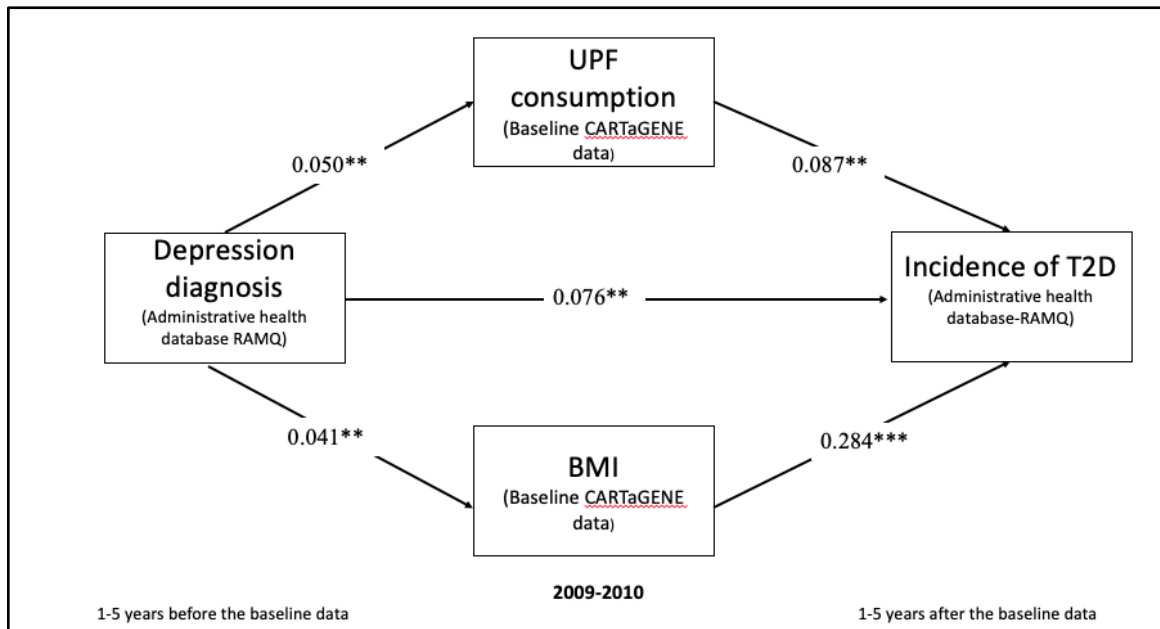
Values shown are standardized regression coefficients from regression-based model. The indirect effect of depression on T2D incidence via UPF consumption (0.048) was statistically significant ($p < 0.01$). The model adjusted for age and sex. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Figure 5.2b Results of single mediation model testing whether the effect depression on type 2 diabetes was mediated by ultra-processed food consumption in fully adjusted model



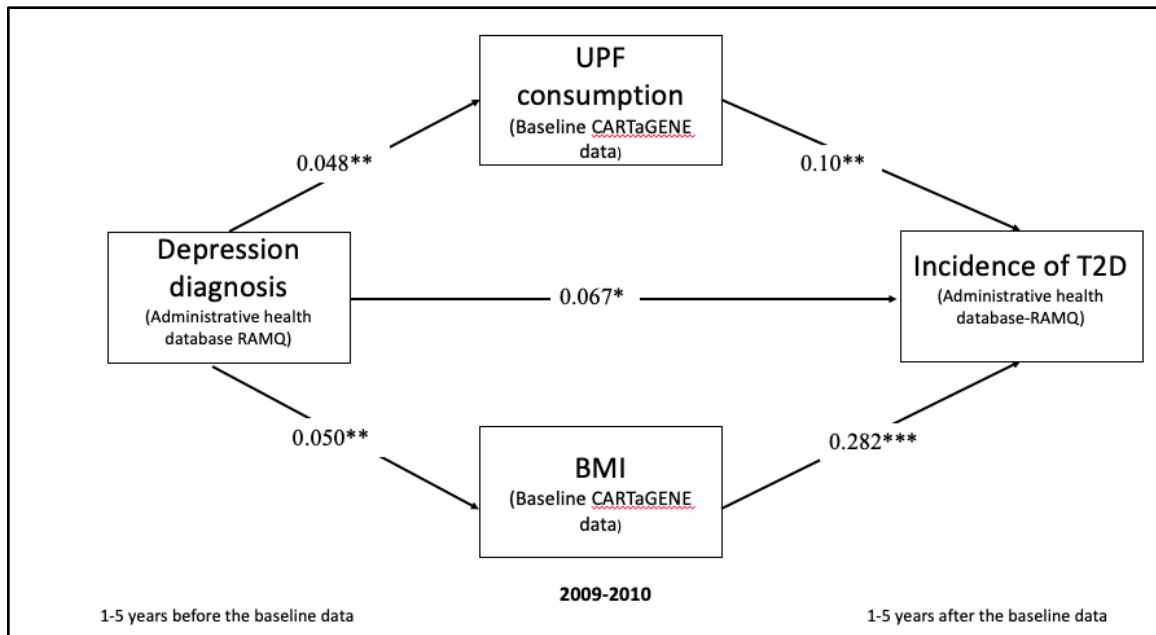
Values shown are standardized regression coefficients from regression-based model. The indirect effect of depression on T2D incidence via UPF consumption (0.005) was statistically significant ($p < 0.05$). The model adjusted for age, sex, educational level, marital status, income, country of birth, physical activity, smoking status, alcohol consumption, Hba1c levels, and BMI. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Figure 5.3a Results of parallel mediation model testing whether the effect of depression on type 2 diabetes incidence was mediated by both ultra-processed food consumption and body mass index in model adjusted for age and sex



Values shown are standardized regression coefficients from regression-based model. The indirect effect of depression on T2D incidence via UPF consumption (0.004) was statistically significant ($p < 0.05$). The indirect effect of depression on T2D incidence via BMI (0.012) was statistically significant ($p < 0.05$). The model adjusted for age and sex. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Figure 5.3b Results of parallel mediation model testing whether the effect of depression on type 2 diabetes incidence was mediated by both ultra-processed food consumption and body mass index in fully adjusted model



Values shown are standardized regression coefficients from regression-based model. The indirect effect of depression on T2D incidence via UPF consumption (0.033) was statistically significant ($p < 0.01$). The indirect effect of depression on T2D incidence via BMI (0.096) was statistically significant ($p < 0.01$). The model adjusted for age, sex, educational level, marital status, income, country of birth, physical activity, smoking status, alcohol consumption, and Hba1c levels. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Chapter 6: Discussion, Implications, and Conclusion

This manuscript-based dissertation was guided by the research question “*What is the relationship between T2D and UPF consumption and depressive symptoms?*” Three research objectives (and hypotheses) were posited and represent different investigative questions. This final chapter begins by summarizing the results reported in each of the standalone scientific articles, one for each research objective (Chapters 3, 4, and 5). Regarding the answer to the overall research question, evidence has been found on a significant relationship among T2D and UPF consumption and depressive symptoms. In short, adults with higher UPF consumption have a higher risk of T2D, and adults with high UPF consumption and depressive symptoms have a higher risk estimate with T2D and its related complications. A general discussion of these results and their implications is followed by a section on the strengths and limitations of the study, culminating with the conclusion to this thesis.

Summary of Tri-Study Results

The first manuscript (Chapter 3) estimated the association between depressive symptoms, UPF consumption, and T2D incidence among the adult population aged 40–69 in Quebec, Canada. This first study (secondary data analysis) included $N=3880$ participants without diabetes from the CARTaGENE baseline study that were followed for up to seven years using data from the provincial health insurance database to determine the T2D incident. Overall, 263 incident diabetes cases were registered in this period (6.7% of the original sample).

Using Cox proportional hazards modelling, a univariate association was initially assessed. To reiterate, an $HR > 1$ suggests an increased risk, and an $HR < 1$ suggests a smaller risk. Individuals who were the highest UPF consumers had the highest risk for T2D incidence with an HR of 1.47 (95 % CI 1.07 - 2.03) compared to the low consumers. Further, elevated depression was

measured using two indicators: the PHQ-9 and the use of the antidepressant medication at the time of the survey. The HR for depressive symptoms ($\text{PHQ-9} \geq 6$) was 1.12 (95 % CI 0.85 - 1.76), and HR for antidepressant use was 1.31 (95 % CI 0.85 - 2.01).

In the first study (Chapter 3), the additive interaction between UPF consumption and depressive symptoms was also evaluated by creating four groups based on the presence and absence of UPF consumption and depressive symptoms. The risk for T2D incidence for respondents with both elevated depression and high UPF consumption at baseline was 1.58 HR (95 % CI 0.93 - 2.68). The risk for T2D incidence when two indicators of depression were combined (depressive symptoms and use of antidepressant use) with high UPF consumption was 1.62 HR (95 % CI 1.02 - 2.57).

In the second manuscript (Chapter 4), we assessed how depressive symptoms and UPF consumption were associated with diabetes-specific complications in adults with T2D. By linking CARTaGENE survey data with administrative health data, the incidence of T2D complications was examined in adult individuals ($N = 683$) with T2D at baseline. In total, $n = 105$ (15%) individuals developed diabetes-related complications over seven years. The Cox proportional hazards model revealed that individuals with depressive symptoms and high UPF consumption at baseline had a higher risk of developing T2D related micro-and macro complications in a model adjusted for sex and age with an HR of 2.43 (95 % CI 1.18 - 4.99) compared to those with depressive symptoms (HR = 1.48; 95 % CI 0.75 - 2.94) only and those with high UPF consumption only (HR = 1.40; 95 % CI 0.90 - 2.20). Similar to study 1 (Chapter 3), the risk was greater for T2D complications when two indicators of depression were combined (depressive symptoms and the use of antidepressant use) with high UPF consumption, showing an HR of 2.59 (95 % CI 1.32 - 5.06) in fully adjusted model.

Results from study 1 and study 2 (Chapters 3 and 4 respectively) confirmed that when risk factors presented in combination or were clustered together, which is often the fact, the risk estimate for developing T2D and its complications incidence was greater than when the risk factors were present alone. As a step further, we wanted to understand the mechanisms between depression and T2D incidence. Depression is often associated with an increased risk of T2D (Graham et al., 2020). This association can be explained partially by lifestyle behaviors (e.g., eating low quality diets), UPF consumption, and higher BMI (Tabák et al., 2014). To explore this question, we performed a mediation analysis in the third study (Chapter 5).

To conduct a mediation analysis, an important requirement is to have a temporal relationship between the predictor, mediator, and outcome with each occurring at different time points (Zhao et al., 2010). Our objective was to assess how much UPF consumption (mediator) would contribute to the relationship between depression (predictor) and T2D incidence (outcome). Further, we also wanted to assess if UPF consumption is still a mediator when considering the potential mediating effect of BMI on the association between depression and diabetes onset. Depression was assessed using diagnostic codes based on the administrative health database five years before the CARTaGENE baseline assessment. Since information on depressive symptoms as measured by PHQ-9 was not available before the CARTaGENE baseline survey. UPF consumption and BMI were assessed at the baseline, and the incidence of diabetes was assessed using the administrative health database after the baseline.

We found that depression diagnosed in administrative database was positively associated with UPF consumption and BMI at the baseline, which were positively associated with the T2D risk in later life. These results suggest that depression diagnosed in administrative database may

partly be related to T2D risk via unhealthy eating behaviours such as high UPF consumption and having a higher BMI.

All results reported in the three studies (Chapters 3, 4, and 5) represent original contributions to the literature and knowledge base. To best of my knowledge, no studies had yet attempted to quantify the excess fraction of incident diabetes and its complications associated with the co-occurrence of (a) one of the most widely occurring psychological issues, i.e., depression, and (b) the behavioral risk factor of UPF consumption. Moreover, this study was unique in its design and presentation of results (three sequential studies), which allowed a more nuanced illustration of how psychological and behavioral factors may work together to increase diabetes risk than has been done to date. These results suggest the following: (a) while depression as a psychological factor may pose a substantial risk to T2D and its complication onset, and (b) important modifiable factors that work in concert with other traditional factors may further increase the disease burden (e.g., eating unhealthy food, and obesity).

Discussion and Implications

Results confirm that adults with higher UPF consumption had a higher risk of T2D, as reported in previous literature (Delpino et al., 2022). Further, adults with high UPF consumption and depression showed a higher risk estimate with T2D and its related complications in a community-based setting.

This evidence has implications for: (a) identifying adults at higher risk of T2D and its complications; (b) preventing diabetes; (c) understanding potential mediating mechanisms between depression and T2D (especially UPF consumption); and (d) future methodological considerations for likeminded research. In short, results from this dissertation have implications for research, policymaking, and public health practice.

Identifying Individuals and Populations at Higher Risk of Type 2 Diabetes

Results can be applied to research, public health, and clinical settings to identify adults with a higher risk of T2D. Study 1 (Chapter 3) focused on the role of UPF consumption and depression on T2D incidence. Results indicate that high UPF consumption can increase the risk of T2D in individuals. Moreover, 50% of UPF contribution came from sugary drinks and beverages. This result encourages clinicians and doctors to heed information about patients' high UPF consumption, particularly sugary drinks, and beverages, to help identify adults at higher risk of T2D across various settings. Given the well-established association between sugary drinks and T2D (Veit et al., 2022), this result holds importance in guiding clinical practice and informing public health interventions.

Results also provide valuable insights into population-level trends and patterns of UPF consumption and highlight that UPF consumption might be an important risk factor behind the current T2D crises (per Delpino et al., 2022). Therefore, policymakers should implement and enforce regulations on the marketing, advertising, and labeling of UPF relative to its connection to T2D incidence. Results (Chapters 3 and 4) also indicate that the risk of T2D and its complications is highest when risk factors are interacting with each other, for example, among individuals with high UPF consumption and depression. This information may aid in identifying individuals and populations at higher risk of T2D and its complications in clinical and public health settings.

The assessment of depression with an emphasis on high UPF consumption should be considered when performing T2D risk assessment inquiries in the future, for example, when conducting the *Canadian Diabetes Risk Questionnaire* (CANRISK). Of note is that research has shown that depression is a heterogeneous and etiologically complex psychiatric syndrome.

Depression can be described as a first episode, recurrent, or chronic episode; it can be mild, moderate, or severe, with or without psychotic features (Buch & Liston, 2021). Clinicians and doctors should remain cognizant of and bear in mind these characteristics of depression when assessing T2D.

To continue, the dysregulation (impairment) of the HPA axis (i.e., a major neuroendocrine system that controls reactions to stress and regulates many body processes), is more commonly observed in chronic depression, where depressive symptoms persist for an extended period. This chronic activation of the stress response system can lead to sustained high levels of cortisol, which may contribute to the development of insulin resistance and increase the risk of T2D over time (Tabák et al., 2014). We assessed the depressive symptoms during the previous two weeks using PHQ-9. It was not possible to perform the distinction between chronic depression and a single episode of depression because data for depressive symptoms were presented only for a one-time point. Therefore, future research should distinguish between subtypes of depression when assessing the risk of T2D.

Preventing Type 2 Diabetes

Results also have implications for T2D prevention. In all three studies (Chapters 3, 4, and 5), we found that depression was linked with an increased risk of T2D. Therefore, identification and treatment for depression should form part of a T2D prevention approach.

Results also highlighted the interaction between depression and UPF consumption. Therefore, future research and applications to clinical practice should consider integrated care that provides treatment for *both* depression and poor behavioral risk factors for T2D (e.g., high UPF consumption). To elaborate, in Canada, the framework for health care is disease-specific, and mental and physical health treatment is often delivered in separate settings (Palladino et al.,

2019; Rosella & Kornas, 2018). I suggest that results herein have a role in emphasizing the need for integrated, patient-centered care that incorporates mental and physical health treatment to support individuals with depression at high risk of T2D. Evidence from collaborative care models for depression and T2D indicate that integrated care of depression and metabolic health may improve health outcomes. These models typically include treatment for depressive symptoms as well as management of T2D and its complications (Atlantis et al., 2014).

These collaborative care models are also effective in reducing depression and improving the quality of life in people with comorbid depression and diabetes (Wang et al., 2022). However, evidence from high-quality studies is needed to determine the effectiveness of collaborative care for depression and the prevention of T2D. Results herein indicate that collaborative care models might aid in identifying and managing specific depressive symptoms, such as a change in appetite, by looking at unhealthy eating patterns, such as UPF consumption, and weight gain.

Mediated Mechanisms Between Depression and Type 2 Diabetes

Results also shed light on proposed mechanisms between depression and T2D. Results from manuscript 3 (Chapter 5) (mediated analysis) showed that depression was associated with behavioral factors that increased the risk of T2D, including eating unhealthy diets, such as UPF, and higher BMI. Measures of depression, risk factors, and T2D were taken at different points in time. Thus, we can say that we directly assessed one of the proposed mechanisms. That said, there might be unexamined *mediators* that link depression with T2D, and these should be researched in the future. One explanation might be high sugar consumption, which can activate brain regions associated with the reward response and provoke a more intense feeling of hunger than in low-sugar diets (Alonso-Alonso et al., 2015). These reward responses can drive the loss

of self-control leading to overeating and subsequent weight gain, which in turn influence the development of T2D (Malik & Hu, 2012).

Results also revealed that 50% of UPF contribution came from sugary drinks and beverages. Studies have shown that excessive sugar intake (a key aspect of UPF) can promote chronic low-grade inflammation (Della Corte et al., 2018). Consumption of sugary foods and beverages can increase inflammatory markers such as CRP and IL-6 (Della Corte et al., 2018). Chronic inflammation is linked to various health conditions, including diabetes and depression (Tabák et al., 2014). Results across the three studies affirmed that further research is needed to better understand lifestyle-related and biological mechanisms between depression and T2D so more effective preventative strategies can be developed. Opportunities for future research especially include developing a nutritional tool that can directly assess UPF consumption and further divide food based on sugar intake.

Methodological Opportunities

As noted, results were obtained using a 93% of sample comprising mainly white respondents (self-reported ethnicity) from Quebec, Canada, and may not generalize to different populations or to other provinces or territories. This research design issue matters because the prevalence of T2D is increasing disproportionately in other populations globally (Schaper et al., 2023). For example, in Canada Indigenous population are at higher risk of T2D than the general population (Diabetes Canada and Diabètes Québec, 2000; Kaczorowski et al., 2009).

Therefore, for future studies, it is recommended to replicate epidemiological analyses in ethnically diverse populations. Examples of surveys that could be considered for such analyses include the Canadian Community Health Survey - Nutrition, the National Health and Nutrition Examination Survey, and the Mexican National Nutrition and Health Survey (Encuesta Nacional

de Salud y Nutrición, ENSANUT). This would give added strength (validity) and broader generalizability and applicability of results. Better yet, the use of harmonized data from these surveys should be considered for cross-study comparison.

Further, due to limitations in the sample size, we could not perform the sex stratification analysis, and research has shown that depression may have distinct associations with T2D risk in men and women (Feng et al., 2023). Women and men cope with depression differently. This sex related difference matters because people's coping mechanisms ultimately affect their diet, physical activity, and diabetes risk (Demmer et al., 2015; Mezuk et al., 2008). One study reported that, compared to men, risk for incidence diabetes was consistently higher among American women with more depressive symptoms (Demmer et al., 2015). Moreover, there is increasing evidence that understanding sex and gender differences is also important in the epidemiology, pathophysiology, treatment, and outcomes of various diseases, with a specific emphasis on noncommunicable diseases (Kautzky-Willer et al., 2016). Gender differences arise from sociocultural processes, such as different behaviors of women and men, exposition to specific influences of the environment, distinct nutritional patterns, lifestyles, stress responses, and attitudes toward treatments and prevention (Kautzky-Willer et al., 2016). It is crucial to recognize that sex and gender are not straightforward binary categories; instead, they represent a spectrum of femininities and masculinities intertwined with other significant sociodemographic variables (Annandale & Riska, 2009). Furthermore, gender roles and identity are shaped by a complex interplay involving genetic, endocrine, and social factors (Kautzky-Willer et al., 2016).

Sex and gender difference analysis may be helpful in integrated care to treat depression and the risk of T2D. Because of the complicated nature of diabetes, this care should include both horizontal integration (multidisciplinary teams) and vertical integration (levels of care – primary,

secondary, and tertiary) (Gröne & Garcia-Barbero, 2002). Integrated care has been found to be especially important for individuals with chronic diseases (Leichsenring, 2004) such as T2D. Diabetes affects approximately 3 million Canadians (about 8% of the population) with upwards of 95% of diabetes cases being T2D (LeBlanc et al., 2019). Studies exploring sex-gender difference analysis and integrated care for diabetes in Canada should thus be considered.

Finally, a growing number of studies independently show the impact of depression (Godos et al., 2023) and UPF consumption (Delpino et al., 2022) on diabetes outcomes. Prior to arriving at similar conclusions to those drawn herein, further research is needed to examine the combined psychological and behavioral risk factor interaction in diabetes outcomes. Type 2 diabetes results from the interaction of many factors (Zou et al., 2017). Psychological factors include anxiety, general stress, sleep disturbance, and depression and its many subtypes (Tabák et al., 2014). Behavioral factors include alcohol and drug consumption, smoking, physical (in)activity, and diet choices including UPF consumption (Nouwen et al., 2019). Research about the “interaction effects between risk factors is meaningful for understanding the pathogenesis and the basic care of type 2 diabetes” (Zou et al., 2017, p. 189).

Strengths and Limitations

The strengths of the research recounted in this dissertation stem from the use of community-based cohorts that were followed up using administrative data. This strategy provided a unique insight into associations between depression, UPF consumption, and T2D. For all three studies, the use of administrative data allowed for considerable follow-up time to determine the incidence of T2D and its related complications. Two benefits of administrative data are that they reduce bias apparent in self-reported measures of T2D incidence and provide time-to-event data that allow for complex survival methods (Muggah et al., 2013).

Using different measures of depression in the survey at the baseline (PHQ-9 and antidepressant use) was also a strength of this dissertation. Depression examination with two different measures enabled us to examine the consistency of multi-study results. Further, in manuscript 1, 439 individuals had a PHQ-9 score greater than 6, and 93 individuals (33%) were using antidepressants. In manuscript 2, among the 683 individuals, 97 individuals (16.6%) had a PHQ-9 score greater than 6, while 586 participants (83.4%) had a PHQ-9 score less than 6. Notably, 18 individuals who had a PHQ-9 score greater than 6, representing 31% of those participants, were taking antidepressant medication. It is important to emphasize that antidepressants represent only one of several treatment options for depression. Psychological interventions, including cognitive-behavioral therapy, interpersonal therapy, and supportive therapy, play a crucial role in effectively managing depression (Health Quality Ontario, 2017). Given that the sample was drawn from the general population rather than the clinical population in the CARTaGENE cohort, it is likely that fewer individuals will exhibit depressive symptoms.

There were also several methodological strengths. Given the considerable follow-up time, I was able to perform complex analyses such as Cox proportional hazard regression, and mediation analysis. Further, to test the robustness of Study 1 and Study 2 (Chapter 3 and 4, respectively), several sensitive analyses were performed.

There are also study limitations to acknowledge. The results may be biased due to non-response to health surveys, as CARTaGENE is a voluntary health survey. Selection bias (i.e., no guarantee of representation) might be related to depression, nutrition component, or covariates such as demographic characteristics and lifestyle behaviors, which can influence results estimates. Selection bias may have been an issue in the CARTaGENE cohort leading to non-responses, an issue beyond our control but still with possible ramifications in this dissertation.

To elaborate, non-responses are often associated with younger age, male sex, lower education levels, and not being married (Korkeila et al., 2001; Veenstra et al., 2006). Non-response also seems to be correlated with health behaviors such as poor nutrition, alcohol use, smoking, and higher BMI (Tolonen et al., 2005; Veenstra et al., 2006). In a Danish health study, when non-respondents were compared with respondents, non-respondents had higher rates of alcohol, drug, and smoking-related mortality and morbidity indicating more health risk behaviors (Christensen et al., 2015). In the CARTaGENE study, 78,036 individuals were directly contacted to participate in Phase A. It was reported that 53,404 were uninterested, 413 could not go, 1,090 felt the site was too far, and 286 did not go out of fear. Specific to selection bias and non-responses, CARTaGENE respondents were more likely to be in older age groups (e.g., 65 to 69) and had higher educational levels (Awadalla 2013). Moreover, in manuscripts 1 and 3, the association between depression and incident T2D may be susceptible to potential bias due to unmeasured confounding related to elevated glucose levels or prediabetes (Deschênes et al., 2016). Elevated glucose levels serve as one of the predictors for the development of T2D. Additionally, in manuscript 2, unmeasured confounders may include the duration of T2D (Zoungas et al., 2014), as these variables were not available in the dataset, we were not able to control for these variables.

Moreover, approximately 7,000 individuals in the CARTaGENE study provided information on the food frequency questionnaire (FFQ), which assessed their nutritional status (Awadalla et al., 2013). Our results may therefore reflect a healthy-respondent effect in the samples used in this dissertation, where respondents may be healthier than the general population (Sanmartin et al., 2016). Nevertheless, response patterns are often complex and may also be

related to disinterest, time to complete a survey, and proximity to the examination site (Awadalla et al., 2013; Tolonen et al., 2017).

Dietary intake in the CARTaGENE survey was measured using FFQ (Awadalla et al., 2013). These tools are commonly used in nutrition research to assess dietary intake over a specified period (Shim et al., 2014). However, these tools also have limitations with two of interest herein. First, FFQs rely on respondents' ability to accurately recall and report their dietary intake over a specific period, which is prone to recall bias. Respondents may modify their reported dietary intake based on social desirability or perceived societal expectations of healthy eating (Briefel et al., 1992). This can lead to overreporting healthy foods and underreporting unhealthy foods thereby biasing the results toward more favorable dietary patterns (Mendez, 2015).

Second, FFQs are prone to measurement errors, including underestimation or overestimation of portion sizes, incomplete food item lists, and imprecise frequency. These measurement errors can lead to misclassification of dietary intake, which can affect the accuracy of associations between diet and health outcomes (Mendez et al., 2015). Further, FFQ was not specifically designed to collect data about the new NOVA classification of UPF consumption. Additionally, there is also limitation related to NOVA classification. Because of its complex and multidimensional definition of levels of food processing, there is a potential for introducing ambiguity and variations in interpretation related to UPF (Braesco et al., 2022). Another notable limitation linked to the approach employed for classifying food items into group 4 of the NOVA classification is single food items categorized as composite dishes, such as baked dishes with multiple ingredients. In this classification process, these composite dishes were not disaggregated into their individual components; rather, they were collectively categorized as a

whole into the ultra-processed foods group of the NOVA classification. CARTaGENE respondents were also limited to mostly white participants (93%) and adult population aged between 40 to 69 years (Awadalla et al., 2013). Therefore, conclusions about the generalizability and external validity of results herein should be made with caution.

There are also limitations of the administrative database. First the follow-up information about the individuals in the administrative database might be lost because individuals might move out of the province, opt for the private healthcare services, and might have died. Further, in Manuscript 3 (Chapter 5), administrative data were used to identify diagnoses of depression in the CARTaGENE cohort before the baseline assessment, which is a strategy that has little concordance with structured diagnostic interviews (Edwards et al., 2020). However, one of issue with the administrative data is the undercoding of depression by physicians which can lead to an incomplete representation of the true prevalence of depression in the database (Cunningham et al., 2014). Approximately 94% of physicians record only one code per claim, and mental health illnesses are coded less often when individuals also present with comorbidities (Cunningham et al., 2014).

Finally, due to the limited sample size, we could not perform a sex stratification analysis. Research has shown that depression may have distinct associations with T2D risk in men and women (Feng et al., 2023). Therefore, future studies should also consider the sex difference analysis, which may also be helpful in integrated care to treat depression and the risk of T2D.

Conclusion

This dissertation provided a detailed, inaugural exploration of the relationship between depression, UPF consumption, and T2D and its complications in the community population in Quebec, Canada. At a macro level, results point to the potential impact of depression on T2D and

its complications. Further, analysis and discussion generated insight into the complexity of this relationship. While depression alone is an important risk factor for diabetes and its complication onset, depression is also associated with substantial increases in diabetes risk in combination with unhealthy eating (e.g., UPF consumption).

Results highlight the importance of understanding how depression, in combination with UPF consumption, can influence the risk of T2D and its complications and how UPF consumption can mediate the relationship between depression and T2D. We found that adults with higher UPF consumption had a higher risk of T2D, and adults with high UPF consumption *and* depression were associated with a higher risk estimate with T2D and its related complications. Results further suggest that the co-occurrence of depression and UPF consumption, each one an independent risk factor for T2D, should be considered *jointly* in population health management.

Finally, results (focused on depression and UPF consumption) can contribute to: (a) improved identification of adults at high risk of T2D; and (b) the development of targeted/tailored T2D prevention strategies. This contribution is significant, as mortality rates among Canadian individuals with diabetes are almost twice as high as those without diabetes. Diabetes affects upwards of 8% of the Canadian population, and virtually (95%) all diabetes cases are Type 2 Diabetes. Evidence-based treatment and prevention strategies are needed to combat this chronic disease with this dissertation contributing to that imperative. Moreover, there is a need to change the environment to conducive to UPF intake.

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Appendices

Appendix 1	Detailed list of food items from Diet History Questionnaire II classified under Nova group 4 as Ultra-processed Foods
Appendix 2	Ethical clearance certificates
Appendix 3	Directed acyclic graph showing the complex association between, depression, ultra-processed food consumption and type 2 diabetes and its complications
Appendix 4	Patient Health Questionnaire-9 (PHQ-9)
Appendix 5	Handling missing data in a Diet History Questionnaire II
Appendix 6	Classification of Diet History Questionnaire food items into the group 4 of NOVA classification

Appendix 1 Detailed list of food items from Diet History Questionnaire II classified under Nova group 4 as Ultra-processed Foods

Question No.	Food items
NUT_5	How often did you have other fruit drinks (such as Fruité, Fruitopia, Five Alive, Sunny D, or Kool-Aid, diet or regular)?
NUT_7	How often did you drink chocolate milk or hot chocolate?
NUT_8	How often did you drink milkshake?
NUT_9	How often did you had meal replacement or high-protein beverages (such as Boost, Breakfast Essential, Ensure, Slimfast or others)?
NUT_10	How often did you soft drinks or pop?
NUT_11	How often did you drink sports drinks?
NUT_12	How often did you energy drinks (such as Red Bull, Rock Star, Full Throttle, or Monster)?
NUT_18	How often did you eat cold cereal?
NUT_54	How often did you eat salad dressing (including low-fat) on salads?
NUT_56	How often did you eat French fries, home fries, hash browned potatoes, or tater tots?
NUT_59	How often did you eat salsa?
NUT_60	How often did you eat ketchup?
NUT_73	How often did you eat bagels or English muffins?
NUT_76	How often did you eat jam, jelly, or honey on bagels, muffins, bread, rolls, or crackers?
NUT_79	How often did you eat turkey or chicken COLD CUTS (such as loaf, luncheon meat, turkey ham, turkey salami, or turkey pastrami)?
NUT_80	How often did you eat luncheon or deli-style ham?
NUT_81	How often did you eat other cold cuts or luncheon meats (such as bologna, salami, corned beef, pastrami, or others, including low-fat)?
NUT_84	How often did you eat beef hamburgers or cheeseburgers from a fast food or other restaurant?

NUT_87	How often did you eat hot dogs, wieners or frankfurters? (Please do not include sausages or vegetarian hot dogs.)?
NUT_99	How often did you eat bacon (including low-fat)?
NUT_100	How often did you eat sausage (including low-fat)?
NUT_104	How often did you eat ready-to-eat battered fish or fish sticks, including in fast food sandwiches (not including shellfish)?
NUT_111	How often did you eat pizza?
NUT_112	How often did you eat crackers?
NUT_113	How often did you eat corn bread or corn muffins?
NUT_114	How often did you eat baking powder biscuits, including scones or tea biscuits?
NUT_115	How often did you eat potato chips (including low-fat, baked, or low-salt)?
NUT_116	How often did you eat corn chips or tortilla chips (including low-fat, baked, or low-salt)?
NUT_118	How often did you eat pretzels?
NUT_122	How often did you eat energy or high-protein bars, (such as Power Bars, Vector, Clif, Luna, Isoflex or others)?
NUT_127	How often did you eat ice cream or ice cream bars (including low-fat or fat-free)?
NUT_128	How often did you eat cake (including low-fat or fat-free)?
NUT_129	How often did you eat cookies or brownies (including low-fat or fat-free)?
NUT_130	How often did you eat doughnuts, sweet rolls, Danish, or Pop-Tarts?
NUT_131	How often did you eat sweet muffins or dessert breads (such as banana bread, blueberry muffins, or lemon loaf, including low-fat or fat-free)?
NUT_134	How often did you eat chocolate candy?
NUT_135	How often did you eat other candy?

The full **Diet History Questionnaire II** is available [here](#)

Appendix 2 Ethical clearance certificates



BY E-MAIL

Montréal, March 02, 2022

Norbert Schmitz, PhD

Full Professor

Department of Psychiatry

McGill University

RE: Annual renewal for the research project 2021-307, "Type 2 diabetes incidence and its association with diet, depressive symptoms, and socioeconomic status in a population-based sample Incidence du diabète de type 2 et son association avec le régime alimentaire, les symptômes dépressifs et le statut socio-économique dans un échantillon de population."

Principal Investigator: Dr. Norbert Schmitz, PhD

Funding organization: Canadian Heart and Stroke Foundation

Dear Dr. Schmitz,

The Research Ethics Board (REB) of the Centre intégré universitaire de santé et de services sociaux (CIUSSS) de l'Ouest-de-l'Île-de-Montréal – Mental Health and Neuroscience subcommittee, which acts as the evaluating REB for the above-mentioned research project, received the documents that you have submitted for the annual renewal of ethics approval. The documents are as follows:

F9H-746 Annual Renewal- Harmonized

- approved documents (REB_annualreport2022_21_05_schmitz-approved.pdf)

It has been determined that the review of your documents could be delegated in accordance with section 6.12 of the Tri-Council Policy Statement (TCPS 2) as there is no information to suggest that the level of risk could have changed. We are happy to inform you that on March 1, 2022, the

REB chair or a delegate reviewed your documents, as well as your responses to our comments, and has re-approved the project.

The ethical approval of your project is therefore renewed from March 1, 2022 to February 23, 2023. The members of the REB will be informed of this decision at the following full board meeting and the decision will be noted in the minutes.

During this renewed approval period, you agree to continue to adhere to the terms outlined in the full ethical and scientific approval letter which are as follows:

- Ensure that the established policies for the identification of research participants are respected. In the CIUSSS de l'Ouest-de-l'Île-de-Montréal, the researcher is responsible for maintaining an up to date list of research participants, which may be transmitted upon request with a minimal delay to the REB or Institution;
- Submit to the REB, for prior approval, all project amendments other than administrative; expect in a case when the amendment is necessary to eliminate an immediate danger to the research participants. In the latter case, the REB should be advised as soon as possible;
- Notify the REB, with minimal delay, of all therapeutic incidents or other serious adverse events that could be related to the experimental medication or natural health product, or, where applicable, all accidents related to the research project's procedures;
- Notify the REB, with minimal delay, of all new information that could affect the ethical nature of the research project, particularly information that could influence an individual's decision to participate in this study;
- Inform the REB, with minimal delay, any suspension or cancellation of authorization ordered by a regulatory body, funding agency or sponsor.
- Inform the REB, with minimal delay, of any modifications pertaining to the clinical equipoise or risk benefit ratio in light of analysis to the data collected;
- Inform the REB, with minimal delay, of any problems identified by a third party over the course of a monitoring or auditing activity, whether internal or external, which may call into question the ethical nature of the project, regardless of the third parties' decision;
- Submit to the REB, with minimal delay, a report concerning any premature, temporary or decisive study interruptions, whether in one site or all sites. The report should indicate the nature and motivation behind the interruption, as well as the potential repercussions on the potential study participants, if applicable;
- Submit to the REB an annual report describing the study's overall progress, one month prior to approval expiration date.
- Submit to the REB, with minimal delay, a final report describing the results of the research study. Properly conserve for a determined period, for the purposes of passive monitoring, all documents related to the research project.

For any questions regarding this decision or your research project, please contact the REB office by phone at 514-761-6131, extension 2708, by e-mail at recherche.comtl@ssss.gouv.qc.ca or via the Nagano platform.

A copy of the letter has also been sent to Akankasha Sen.

Thank you for your attention to this matter,



Fredrick Vokey, MA

Agent de planification, programmation et recherche – éthique de la recherche

Direction des affaires universitaires, enseignement et recherche

CIUSSS de l'Ouest-de-l'Île-de-Montréal

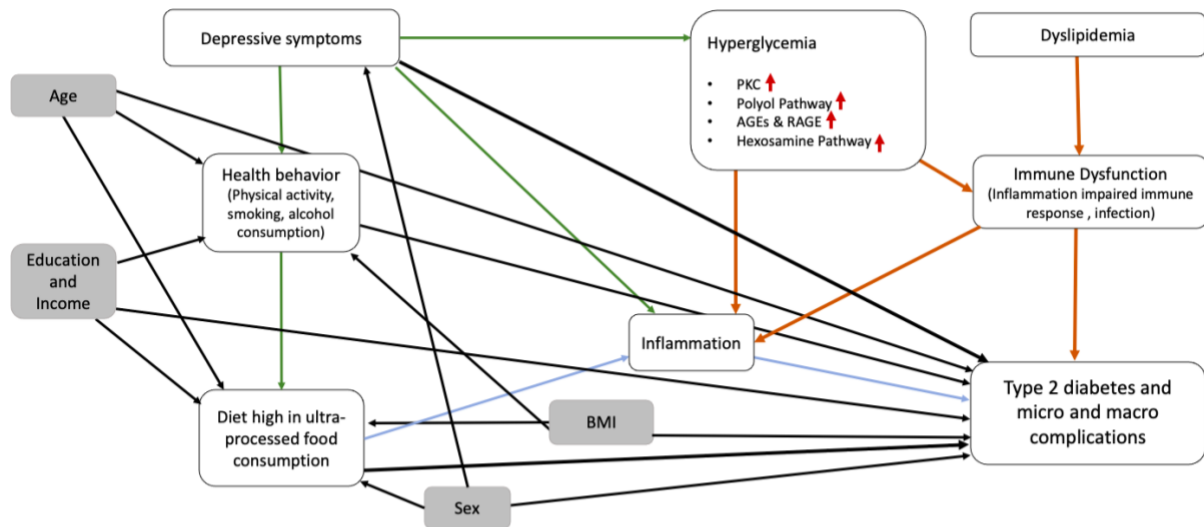
On behalf of:

Joseph Rochford, PhD

Chair, Research Ethics Board – Mental Health and Neuroscience subcommittee

CIUSSS de l'Ouest-de-l'Île-de-Montréal

Appendix 3 Directed acyclic graph showing the complex association between, depression, ultra-processed food consumption and type 2 diabetes and its complications.



Directed acyclic graph (DAG) for the relationship between ultra-processed food consumption, depressive symptoms on development of type 2 diabetes and its complications. An arrow from a factor to another means possible association. The grey-colored box factors are confounders and will be adjusted in the analysis. Biological mechanisms of diabetic complications were also included in the figure; however, variables of the biological mechanisms will not be included in the main analyses. Destruction of pancreatic B cells and insulin resistance in T2DM result in hyperglycemia. The resulting increase of intracellular glucose in microvascular target cells, such as capillary endothelial cells, causes ROS production in the mitochondria, activating four pathogenic downstream pathways: polyol pathway, AGEs & RAGE pathway, PKC pathway, hexosamine pathway. Impaired immune response and consequently higher susceptibility for infections, this immune dysfunction plays a pivotal role in the development of diabetes and its complications. Moreover, insulin resistance and circulating FFAs result in dyslipidemia, contributing to both micro- and macrovascular complications. All these processes mainly exert their harmful effects by upregulation of a pro-inflammatory state at vulnerable sites. Together with an impaired immune response and consequently higher susceptibility for infections, this immune dysfunction plays a pivotal role in the development of diabetic and its complications. Abbreviation; BMI; Body Mass Index, PKC, Protein Kinase C; (R)AGEs, (Receptor for) Advanced Glycation End products; ROS, Reactive Oxygen Species; FFAs, Free Fatty Acids.

Appendix 4 Patient Health Questionnaire-9 (PHQ-9)

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)				
Over the <u>last 2 weeks</u> , how often have you been bothered by any of the following problems? (Use "✓" to indicate your answer)				
	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3
FOR OFFICE CODING <u>0</u> + _____ + _____ + _____ =Total Score: _____				
If you checked off <u>any</u> problems, how <u>difficult</u> have these problems made it for you to do your work, take care of things at home, or get along with other people?				
Not difficult at all ☐	Somewhat difficult ☐	Very difficult ☐	Extremely difficult ☐	

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

Appendix 5 Handling missing data in a Diet History Questionnaire II

Zero imputation was employed to deal with missing data in our data based on the assumption that food item which left blank in the data is not consumed by the respondent. Food frequency questionnaires (FFQ), such as the Diet History Questionnaire II (DHQII), are widely used instruments to assess dietary information in epidemiological research (1). Similar to any long and self-administered questionnaire, FFQ is often associated with non-responses. Therefore, it becomes challenging to estimate the dietary intake from the FFQ (2). Food items on an FFQ might be omitted for different reasons; for example, the food may not be consumed by respondents or difficulties remembering the frequency and amount of intake (3,4).

Various approaches exist for handling missing data in FFQs, including complete case analysis, single imputation (filling in missing values with a single value like mean, median, or zero), and multiple imputation (4). Although most commonly used strategy for handling non-response data in FFQ is zero imputation. Because the common assumption is that participants who did not provide the answer to food items represent zero-intake (1-4).

Various studies obtained information on omitted food items of an FFQ by recontacting the survey participants who omitted food items to verify the zero-intake assumption (4). In a large cohort of Nurses' Health Study II, resurvey of the participants indicated that 64% of the initially omitted foods were never consumed or consumed less than once per month (3). Further, in the Swedish study, omitted answers on FFQ corresponded to very rare consumption in about 54% of participants (1). However, zero imputation can introduce bias because not all missing values may be zero. A common practice of setting missing food items to zero intakes is often not correct and

does not attempt to impute the best estimate of true intake; nevertheless, it does represent a reasonably good estimate (4).

Another approaches, multiple imputation, is effective when missing data are assumed to be missing at random (MAR: the probability that the data are missing does not depend on any data) (50). However, researchers have noted that missing data in FFQ are likely to be missing not at random (MNAR: the probability that data are missing depends on the missing values themselves as well as on the observed data) (6). Multiple imputation may offer a more accurate estimate when the probability of missing data is less than 10% in FFQs (3). A recent study comparing multiple imputation and zero imputation methods for handling missing data in FFQs found slight differences in estimated total energy and nutrient intakes between the two methods (7).

Reference:

1. Hansson LM, Galanti MR. Diet-associated risks of disease and self-reported food consumption: how shall we treat partial nonresponse in a food frequency questionnaire?. *Nutrition and cancer*. 2000 Jan 1;36(1):1-6.
2. Molag ML, de Vries JH, Ocké MC, Dagnelie PC, van den Brandt PA, Jansen MC, van Staveren WA, van't Veer P. Design characteristics of food frequency questionnaires in relation to their validity. *American journal of epidemiology*. 2007 Dec 15;166(12):1468-78.
3. Michels KB, Willett WC. Self-administered semiquantitative food frequency questionnaires: patterns, predictors, and interpretation of omitted items. *Epidemiology (Cambridge, Mass.)*. 2009 Mar;20(2):295.
4. Lamb KE, Olstad DL, Nguyen C, Milte C, McNaughton SA. Missing data in FFQs: Making assumptions about item non-response. *Public health nutrition*. 2017 Apr;20(6):965-70.
5. Klebanoff MA, Cole SR. Use of multiple imputation in the epidemiologic literature. *American journal of epidemiology*. 2008 Aug 15;168(4):355-7.
6. Parr CL, Hjartåker A, Scheel I, Lund E, Laake P, Veierød MB. Comparing methods for handling missing values in food-frequency questionnaires and proposing k nearest neighbours imputation: effects on dietary intake in the Norwegian Women and Cancer study (NOWAC). *Public health nutrition*. 2008 Apr;11(4):361-70.
7. Ichikawa M, Hosono A, Tamai Y, Watanabe M, Shibata K, Tsujimura S, Oka K, Fujita H, Okamoto N, Kamiya M, Kondo F. Handling missing data in an FFQ: multiple imputation and nutrient intake estimates. *Public health nutrition*. 2019 Jun 1;22(8):1351-60.

Appendix 6 Classification of Diet History Questionnaire food items into the group 4 of NOVA classification

The CARTaGENE survey used the Diet History Questionnaire (DHQII) to evaluate nutritional information. Food and beverage items were categorized according to the NOVA (not an acronym) classification system, which considers physical, biological, and chemical modifications occurring post-separation from the natural form of foods. The NOVA classification considers the extent and purpose of processing of the food item and includes four groups – (1) unprocessed or minimally processed food, (2) processed culinary ingredients, (3) processed foods and (4) ultra-processed foods. Main group of our interest was ultra-processed food.

Adopted Strategy:

The strategy replicated the approach published by Khandpur et al. for categorizing ultra-processed foods in large-scale cohorts like Nurses' Health Studies, The Health Professionals Follow-up Study, and Growing Up Today Studies, utilizing a Food Frequency Questionnaire (FFQ) (1).

Four-Stage Identification Process:

Compilation in Excel: All DHQII food items were systematically compiled in an Excel spreadsheet.

Independent Assignment to NOVA Group 4: Two researchers independently assigned foods to NOVA group 4 based on processing grades. One of the researchers was registered dietitian of Canada. Assignment was guided by NOVA classification definitions, examples, and supplementary materials from proponents (2) and other cohorts which were using the FFQ to assess the food items (1). Consensus between both researchers led to the final assignment of food items to their NOVA group. Items flagged for further scrutiny in case of categorization disagreements or uncertainties.

Iterative Review and Consistency: The categorization process was iterative, necessitating a review of the original DHQII. Food preparations from multiple ingredients in the DHQII were not disaggregated. Nutrient profiles, consumption amounts, and participant demographics were not considered. Original food items in the DHQII were categorized in their entirety.

Flagging for Further Scrutiny: In cases of categorization disagreements between researchers or if a researcher was unable to assign a food item to a NOVA group, the item was flagged.

Shortlisting for additional review and resolution occurred for flagged items. Resolution was made by searching the items in different cohort and in which NOVA group they were assigned. The items we categorized in NOVA group 4 were consistently classified in the same group for other cohorts such as Nurses' Health Studies, The Health Professionals Follow-up Study, and Growing Up Today Studies (2).

This meticulous four-stage process ensures a systematic, guided, and iterative approach to categorizing food items based on the NOVA classification system, maintaining consistency and reliability in identifying ultra-processed foods.

Reference:

1. Khandpur N, Rossato S, Drouin-Chartier JP, Du M, Steele EM, Sampson L, Monteiro C, Zhang FF, Willett W, Fung TT, Sun Q. Categorising ultra-processed foods in large-scale cohort studies: evidence from the Nurses' Health Studies, the Health Professionals Follow-up Study, and the Growing Up Today Study. *Journal of Nutritional Science*. 2021;10:e77.
2. Monteiro CA, Cannon G, Levy RB, Moubarac JC, Louzada ML, Rauber F, Khandpur N, Cediel G, Neri D, Martinez-Steele E, Baraldi LG. Ultra-processed foods: what they are and how to identify them. *Public health nutrition*. 2019 Apr;22(5):936-41.